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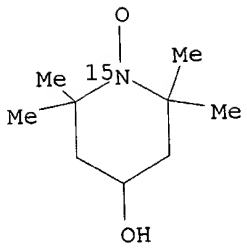
=> s tempol

L4 5 TEMPOL

=> d l4 1-5

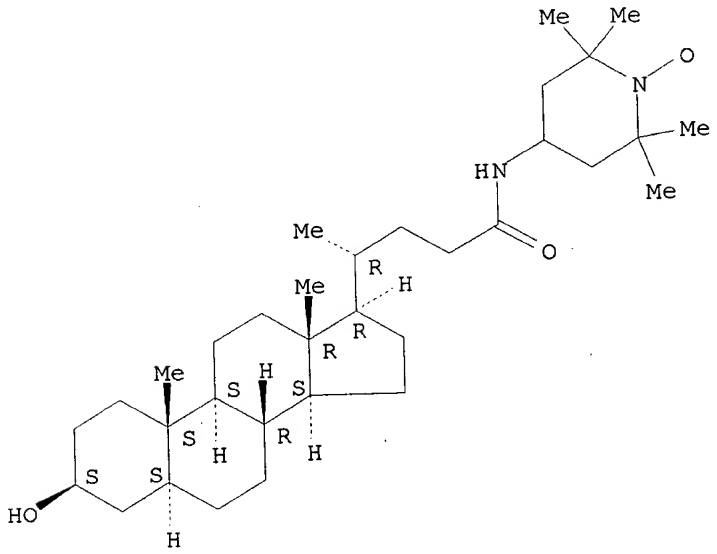
L4 ANSWER 1 OF 5 REGISTRY COPYRIGHT 2001 ACS
RN 79494-16-9 REGISTRY
CN 1-Piperidinyl-1-15N-oxy, 4-hydroxy-2,2,6,6-tetramethyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **15N-TEMPOL**
MF C9 H18 N O2
LC STN Files: CA, CAPLUS, CHEMCATS



4 REFERENCES IN FILE CA (1967 TO DATE)
4 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L4 ANSWER 2 OF 5 REGISTRY COPYRIGHT 2001 ACS
RN 51706-65-1 REGISTRY
CN 1-Piperidinyloxy, 4-[[(3.beta.,5.alpha.)-3-hydroxy-24-oxocholan-24-yl]amino]-2,2,6,6-tetramethyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Cholane, 1-piperidinyloxy deriv.
OTHER NAMES:
CN **4-Lithocholamidotempol**
FS STEREOSEARCH
MF C33 H57 N2 O3
LC STN Files: CA, CAPLUS, TOXLIT

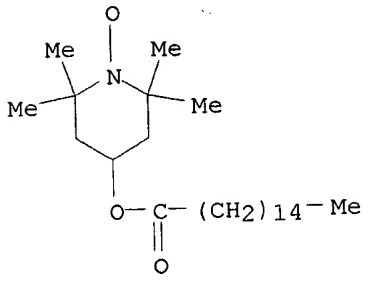
Absolute stereochemistry.



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

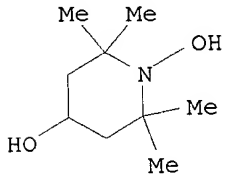
L4 ANSWER 3 OF 5 REGISTRY COPYRIGHT 2001 ACS
RN 42585-25-1 REGISTRY
CN 1-Piperidinyloxy, 2,2,6,6-tetramethyl-1-[(1-oxohexadecyl)oxy]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 2,2,6,6-Tetramethyl-4-oxy-1-oxylpiperidine stearate
CN 4-(Hexadecanoyloxy)-2,2,6,6-tetramethylpiperidine-1-oxy
CN **Tempol palmitate**
MF C25 H48 N O3
CI COM

LC STN Files: BEILSTEIN*, CA, CAPLUS, TOXLIT, USPATFULL
(*File contains numerically searchable property data)



38 REFERENCES IN FILE CA (1967 TO DATE)
38 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L4 ANSWER 4 OF 5 REGISTRY COPYRIGHT 2001 ACS
RN 3637-10-3 REGISTRY
CN 4-Piperidinol, 1-hydroxy-2,2,6,6-tetramethyl- (7CI, 8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN 1,4-Dihydroxy-2,2,6,6-tetramethylpiperidine
CN **Tempol H**
CN TOLH
FS 3D CONCORD
DR 87220-69-7
MF C9 H19 N O2
CI COM
LC STN Files: BEILSTEIN*, BIOSIS, CA, CAOLD, CAPLUS, CASREACT, CHEMCATS, DETHERM*, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

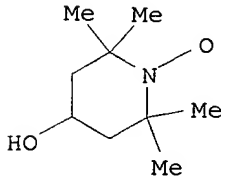


6x-60

75 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
75 REFERENCES IN FILE CAPLUS (1967 TO DATE)
7 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L4 ANSWER 5 OF 5 REGISTRY COPYRIGHT 2001 ACS
RN 2226-96-2 REGISTRY
CN 1-Piperidinyloxy, 4-hydroxy-2,2,6,6-tetramethyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 1-Oxyl-2,2,6,6-tetramethyl-4-hydroxypiperidine
CN 1-Oxyl-2,2,6,6-tetramethyl-4-piperidinol
CN 2,2,6,6-Tetramethyl-1-oxy-4-hydroxypiperidine
CN 2,2,6,6-Tetramethyl-4-hydroxy-1-piperidinyloxy radical
CN 2,2,6,6-Tetramethyl-4-hydroxylpiperidine-1-oxyl
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidin-1-oxyl
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidine 1-oxide radical
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidine oxide
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidine-1-hydroxyl
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidine-1-oxyl
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidine-1-oxyl radical

CN 2,2,6,6-Tetramethyl-4-hydroxypiperidinooxy
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidinooxy radical
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidinyl-1-oxy
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidinyl-1-oxyl
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidinyloxy radical
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidinyloxyl radical
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidyl 1-oxyl
CN 2,2,6,6-Tetramethyl-4-oxypiperidine-1-oxyl
CN 2,2,6,6-Tetramethyl-4-piperidinol 1-oxide
CN 2,2,6,6-Tetramethyl-4-piperidinol 1-oxyl
CN 2,2,6,6-Tetramethyl-4-piperidinol N-oxyl
CN 2,2,6,6-Tetramethyl-4-piperidinol nitroxide
CN 2,2,6,6-Tetramethyl-4-piperidinol-1-oxy
CN 2,2,6,6-Tetramethyl-4-piperidinol-1-oxyl radical
CN 2,2,6,6-Tetramethylpiperidine-4-hydroxy-1-oxyl
CN 2,2,6,6-Tetramethylpiperidine-N-oxyl-4-ol
CN 2,2,6,6-Tetramethylpiperidinol-4-oxyl-1
CN 4-Hydroxy-1-oxyl-2,2,6,6-tetramethylpiperidine
CN 4-Hydroxy-2,2,6,6-tetramethyl-1-piperidinoxy
CN 4-Hydroxy-2,2,6,6-tetramethyl-1-piperidinoxyl
CN 4-Hydroxy-2,2,6,6-tetramethyl-1-piperidinyloxy
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidine 1-oxide radical
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidine N-oxide
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidine-N-oxy
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidino-1-oxyl
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidinooxy
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidinooxy radical
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidinoxy
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidinoxyl
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidinyl-1-oxyl
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidinyl-N-oxy
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidinyl-N-oxyl
CN 4-Hydroxy-2,2,6,6-tetramethylpiperidyl-1-oxyl
CN 4-hydroxy-TEMPO
CN 4-Oxypiperidol
CN 4H-Tempo
CN HTEMPO
CN **Tempol**
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
DR 13075-58-6, 3174-32-1, 105269-77-0, 119227-61-1, 68541-96-8, 70939-25-2, 38854-37-4
MF C9 H18 N O2
CI COM
LC STN Files: ADISINSIGHT, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DETHERM*, DRUGU, EMBASE, GMELIN*, IFICDB, IFIPAT, IFIUDB, IMSDIRECTORY, MEDLINE, MSDS-OHS, NIOSHTIC, PIRA, RTECS*,
TOXLINE, TOXLIT, ULIDAT, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)



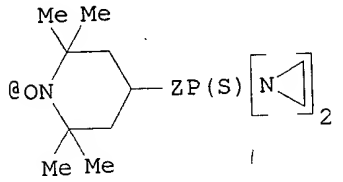
1672 REFERENCES IN FILE CA (1967 TO DATE)
43 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1681 REFERENCES IN FILE CAPLUS (1967 TO DATE)
24 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

AUTHOR(S): Gutierrez, Peter L.; Konieczny, Maria; Sosnovsky, George

CORPORATE SOURCE: Lab. Clin. Biochem., Natl. Cancer Inst., Baltimore, MD, 21201, USA

SOURCE: Z. Naturforsch., B: Anorg. Chem., Org. Chem. (1981), 36B(12), 1612-17
CODEN: ZNBAD2; ISSN: 0340-5087

DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I, Z=O
II, Z=NH

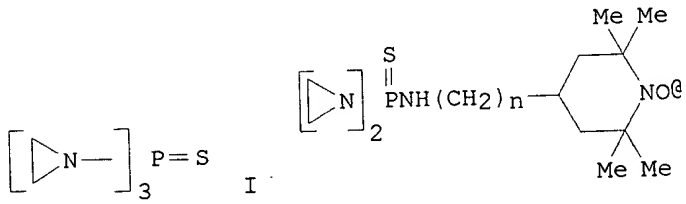
AB The spin-labeled analog of thio-TEPA, 1-oxyl-2,2,6,6-tetramethyl-4-piperidyl-N,N,N',N'-bis(ethylene)phosphorodiamidothioate (SL-O-TT)(I) [51526-59-1], which contains a nitroxyl free radical linked by an O bridge to P, has antitumor properties against P388 murine leukemia (T/C = 242) and a higher therapeutic ratio (5.15) than its parent compd., thio-TEPA (2.75). The drug is less toxic to P388 cells in culture as judged by the [3H]thymidine uptake. On the basis of ESR spectroscopy using L1210 cells incubated with SL-O-TT, the drug appears to bind to cells in culture in such a way as to restrict th motion of the nitroxyl label. A second spin-labeled analog, 1-oxyl-2,2,6,6-tetramethyl-4-aminopiperidyl-N,N,N',N'-bis(ethylene)phosphorodiamidothioate (SL-NH-TT)(II) [33683-34-0] contg. a nitroxyl label linked by a N bridge to P was prepd. by an improved procedure in 95% yield. In vivo results indicate that this analog has about the same therapeutic value (2.73) as Thio-TEPA (2.75), and that higher doses of this compd. are required than those for both the O-bridged analog and Thio-TEPA to achieve max. T/C values.

L4 ANSWER 88 OF 93 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 26

ACCESSION NUMBER: 1979:449273 CAPLUS
DOCUMENT NUMBER: 91:49273
TITLE: Effect of thiophosphamide, its paramagnetic analogs and iminoxyl radical on **tumor** cell division

AUTHOR(S): Kiseleva, E. G.; Konovalova, N. P.
CORPORATE SOURCE: Inst. Chem. Phys., Moscow, USSR
SOURCE: Vopr. Onkol. (1978), 24(4), 60-5
CODEN: VOONAW; ISSN: 0507-3758

DOCUMENT TYPE: Journal
LANGUAGE: Russian
GI

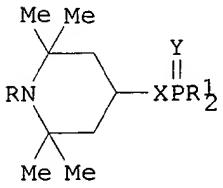


I

II, n=0
III, n=1

related to the formation of toxic products of mol. O in biomembranes.

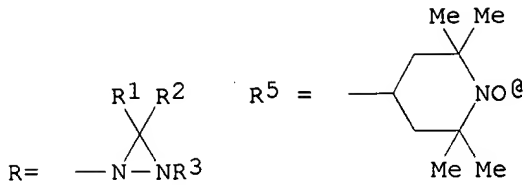
L4 ANSWER 84 OF 93 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1984:210004 CAPLUS
DOCUMENT NUMBER: 100:210004
TITLE: In the search for new anticancer drugs. 9. Synthesis and anticancer activity of spin-labeled analogs of N,N:N',N':N",N"-tris(1,2-ethanediyl)phosphoric triamide and N,N:N',N':N",N"-tris(1,2-ethanediyl)phosphorothioic triamide
AUTHOR(S): Sosnovsky, George; Paul, Buddha D.
CORPORATE SOURCE: Dep. Chem., Univ. Wisconsin, Milwaukee, WI, 53201, USA
SOURCE: J. Med. Chem. (1984), 27(6), 782-8
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

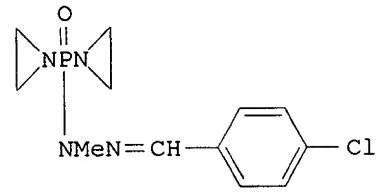


I

AB A no. of title derivs. contg. either 2 aziridine moieties (I; R = H, O.bul., OH; X = NH, NMe, O2CNH; Y = O, S; R1 = aziridino) were synthesized and tested against lymphocytic leukemia P388 in mice. A structure-activity comparison showed that, at optimum dose, all compds. contg. the nitroxyl radical were more active than the corresponding hydroxylamine derivs. The open-chain compds. I (R1 = NHCH2CH2Cl) were less active than the corresponding aziridine ring compds. Replacement of the X-NH bridge in I (R = aziridino) with the X:NMe group lowered the anticancer activity.

L4 ANSWER 85 OF 93 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1984:6646 CAPLUS
DOCUMENT NUMBER: 100:6646
TITLE: In the search for new anticancer drugs. III. Phosphorylated diaziridine derivatives
AUTHOR(S): Sosnovsky, George; Lukszo, Jan
CORPORATE SOURCE: Dep. Chem., Univ. Wisconsin, Milwaukee, WI, 53201, USA
SOURCE: Z. Naturforsch., B: Anorg. Chem., Org. Chem. (1983), 38B(7), 884-94
CODEN: ZNBAD2; ISSN: 0340-5087
DOCUMENT TYPE: Journal
LANGUAGE: English
GI





IV

AB Treating RH (R1 = Me, H; R2 = Me, Et; R3 = CHMe2, Bu, Et) with (EtO)2P(O)Cl or (EtO)2P(O)H-CCl4 gave RP(O)(OEt)2 (I). However, treating 4-R4C6H4CH:NMe (R4 = H, Cl) with H2NOSO3H followed by phosphorylation gave rearranged products 4-R4C6H4CHN:NHMe rather than the expected diaziridines. Treating R5OH with RH [R1 = R2 = R3 = Me; R1R2 = (CH2)5, R3 = H] and P(O)Cl3 gave R5OP(O)R2 (II). P(O)Cl3 reacted with RH [R1R2 = (CH2)5, R3 = H] to give R3P(O) (III). Phosphorylated aziridines such as IV were also prepd. I (R1 = H, R2 = Me, R3 = Et), II (R1 = R2 = R3 = Me), and III were inactive against lymphocytic leukemia P388 in mice at 30-40 mg/kg i.p. daily for 9 days. However IV gave a 94% increase in life span at 32 mg/kg under the same conditions.

L4 ANSWER 86 OF 93 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1983:3195 CAPLUS
DOCUMENT NUMBER: 98:3195
TITLE: Phytohemagglutin-induced changes in spin label reduction in lymphocytes from **tumor**-bearing rats
AUTHOR(S): Hedrick, W. R.; Zimbrick, J. D.; Mathew, A.
CORPORATE SOURCE: Radiat. Biophys. Program, Univ. Kansas, Lawrence, KS, 66045, USA
SOURCE: Biochem. Biophys. Res. Commun. (1982), 109(1), 180-5
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Spin-labeling techniques were utilized to investigate the rate of redn. of spin probes introduced into lymphocytes from normal and **tumor**-bearing animals. The response of the lymphocytes to phytohemagglutinin (PHA) stimulation was monitored by the spin labels Tempone (2,2,6,6-tetramethyl-4-oxopiperidinooxy), PCA (2,2,5,5-tetramethyl-1-pyrrolidinyloxy-3-carboxylic acid), and TMPN (2,2,6,6-tetramethylpiperidinooxy). The EPR signal intensity of the nitroxide spin labels decreased according to 1st-order kinetics. In PHA-challenged lymphocytes from **tumor**-bearing animals, the Tempone signal loss was 2-fold less than that in the corresponding controls.

L4 ANSWER 87 OF 93 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1982:79556 CAPLUS
DOCUMENT NUMBER: 96:79556
TITLE: In the search for new anticancer drugs. II. Antitumor activity, toxicity and electron spin resonance of spin labeled thio-TEPA derivatives

ACCESSION NUMBER: 2000:720111 CAPLUS
DOCUMENT NUMBER: 134:36766
TITLE: The **nitroxide** Tempol induces oxidative stress, p21WAF1/CIP1, and cell death in HL60 cells
AUTHOR(S): Gariboldi, M. B.; Rimoldi, V.; Supino, R.; Favini, E.; Monti, E.
CORPORATE SOURCE: Section of Pharmacology, Department of Structural and Functional Biology, University of Insubria, Varese, Milan, Italy
SOURCE: Free Radical Biology & Medicine (2000), 29(7), 633-641
CODEN: FRBMEH; ISSN: 0891-5849
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The antiproliferative effect of Tempol, a stable **nitroxide** free radical, was investigated on the p53-neg. human leukemia cell line HL60. A concn.- and time-dependent inhibition of cell growth was obsd. that appears to be due to induction of apoptosis. Involvement of oxidative stress is indicated by a concn.-dependent increase in intracellular peroxides and a parallel decrease in total cellular glutathione; in addn., increased survival rates were obsd. in cells simultaneously treated with Tempol and the antioxidant N-acetylcysteine. Tempol did not affect the relative levels of Bax and Bcl2, whereas p21WAF1/CIP1 was enhanced in a concn.- and time-dependent fashion; this effect was partially inhibited by N-acetylcysteine, was maintained for up to 8 h after Tempol removal, and seemed to depend on continuing protein synthesis. The increase in p21WAF1/CIP1 was accompanied by a parallel accumulation of cells in the G1 phase of the cycle and by a decrease in the 110 kDa form of pRb. Our results suggest that p53-independent induction of p21WAF1/CIP1 mediates the antiproliferative effect of Tempol; on the basis of this observation, the **nitroxide** could be proposed as an useful adjunct to the treatment of p53-deficient **tumors**, which are often refractory to std. chemotherapy.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ACCESSION NUMBER: 1993:439950 CAPLUS
DOCUMENT NUMBER: 119:39950
TITLE: Nitroxyl radicals for **cancer** chemotherapy
AUTHOR(S): Emanuel, N. M.; Konovalova, N. P.
CORPORATE SOURCE: Inst. Chem. Phys., Moscow, 117977, Russia
SOURCE: Bioact. Spin Labels (1992), 439-60. Editor(s): Zhdanov, Renat I. Springer: Berlin, Germany. CODEN: 58QYAZ
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English

AB A review with 48 refs. The differences in the chemotherapeutic properties of spin-labeled analogs of antitumor agents and their parent compds. were proved by a no. of examples. The reasons for these differences are not clear enough yet. Presumably, nitroxyl radicals make cells more sensitive to the damaging action of cytotoxic moiety, as is the case with the effect of radiation, which becomes more pronounced when combined with the action of a nitroxyl radical.

ACCESSION NUMBER: 1993:254628 CAPLUS
DOCUMENT NUMBER: 118:254628
TITLE: Preparation of modified bacteriochlorophylls for diagnosis and treatment of **tumors**
INVENTOR(S): Scheer, Hugo; Struck, Andreas; Porra, Robert
PATENT ASSIGNEE(S): Germany
SOURCE: Ger. Offen., 13 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 4121876	A1	19930114	DE 1991-4121876	19910702

OTHER SOURCE(S): MARPAT 118:254628
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. [I, II, and III; M = H, metal atom; R1 = residue of a polyethylene glycol, a (cyclo)aliph. alc., a hydroxylated amino acid, a sugar alc., a hydroxylated lipid, a linear polyol, an aminoalc., a hydroxycarboxylic acid, a **nitroxide**-contg. alc., a chromophore-contg. alc., or a alkylbenzyl alc; R2 = H, OH, CO2R4; R3 = H, OH, alkyl, alkoxy; R4 = (cyclo)alkyl], were prepd. for diagnosis or treatment of **tumors** (no data). Thus, I (R1 = phytyl, R2 = CO2Me, R3 = H) was heated with F3C(CH2)3OH and diazabicycloundecane to give 40% I [R1 = F3C(CH2)3, R2 = CO2Me, R3 = OH]. Title compds. have absorptions up to .apprx.800 nm.

L5 ANSWER 26 OF 91 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:750150 CAPLUS
DOCUMENT NUMBER: 123:137666
TITLE: Effect of gallium-porphyrin analog ATX-70 on **nitroxide** formation from a cyclic secondary amine by ultrasound: on the mechanism of sonodynamic activation
AUTHOR(S): Miyoshi, Norio; Misik, Vladimir; Fukuda, Masaru; Riesz, Peter
CORPORATE SOURCE: National Cancer Institute, National Institutes Health, Bethesda, MD, 20892, USA
SOURCE: Radiat. Res. (1995), 143(2), 194-202
CODEN: RAREAE; ISSN: 0033-7587
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Sonodynamic therapy is a promising new modality for **cancer** treatment based on the synergistic effect on **tumor** cell killing by combination of a drug (typically a photosensitizer) and ultrasound. The mechanism of sonodynamic action was suggested to involve photoexcitation of the sensitizer by sonoluminescent light, with subsequent formation of singlet oxygen. In this work we studied the aq. sonochem. reactions of the gallium-porphyrin deriv. ATX-70, one of the most active sonodynamic agents found, using 50 kHz ultrasound. Th expts. were carried out in the presence of 2,2,6,6-tetramethyl-4-piperidone hydrochloride (TMP), which reacts with singlet oxygen or .bul.OH radicals to give the EPR-detectable **nitroxide** 2,2,6,6-tetramethyl-4-piperidone-N-oxyl (TMP-NO). Recently it has been suggested that the enhancement of TMP-NO yields in the presence of aq. solns. of ATX-70 exposed to ultrasound was evidence for the formation of singlet oxygen in the system. Our results show that the surfactant cetyltrimethylammonium bromide (CTAB) can mimic the ATX-70-induced increase in the TMP-NO signal, but it fails to reproduce the behavior of ATX-70 in D2O: while the yields of TMP-NO in the presence of ATX-70 increase in D2O, the opposite effect was found with the surfactant CTAB. However, our data show that the increased TMP-NO yields in D2O are paralleled by an increased concn. of ATX-70 dimer, a form that is inactive in the photochem. generation of singlet oxygen. Our finding that the ATX-70-dependent enhancement of the TMP-NO signal was highest at .apprx.20% O2, in both N2/O2 and argon/O2 mixts., and decreased with increasing oxygen concn. is not compatible with the singlet oxygen mechanism. Finally, our results on the temp. dependence of the ATX-70-induced formation of TMP-NO are not consistent with the photochem. excitation of ATX-70 by sonoluminescent light: the ATX-70-dependent enhancement of TMP-NO signal increased with temp. in the range 10-25.degree.C, while the intensity of sonoluminescence of aq. solns. both in multiple-bubble fields and in single-bubble expts. is known to decrease with increasing temp.

ACCESSION NUMBER: 1998:301755 CAPLUS
DOCUMENT NUMBER: 129:23078
TITLE: Antiproliferative effect of the piperidine **nitroxide** TEMPOL on neoplastic and nonneoplastic mammalian cell lines
AUTHOR(S): Gariboldi, Marzia B.; Lucchi, Simona; Caserini, Claudia; Supino, Rosanna; Oliva, Cesare; Monti, Elena
CORPORATE SOURCE: Applied Pharmacology Section, Institute of Pharmacology, University of Milan, Milan, Italy
SOURCE: Free Radical Biology & Medicine (1998), 24(6), 913-923
CODEN: FRBMEH; ISSN: 0891-5849
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The stable **nitroxide** 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPOL) is widely used as a probe in biophys. studies and as an antioxidant in several exptl. models. The potential cytotoxic effects of TEMPOL were tested on a panel of human and rodent cell lines, and the **nitroxide** proved to be significantly more effective in inhibiting the growth of neoplastic than nonneoplastic cell lines after a 96-h exposure. More detailed studies on MCF-7/WT cells indicate that at least 24 h are necessary for TEMPOL to induce irreversible cell damage, which seems to be related to the reactivity of the nitroxyl group. This observation, together with the antagonistic effect of N-acetylcysteine, suggests an involvement of free radical-mediated processes. Cell cycle studies indicate a biphasic effect of TEMPOL, with a short-term accumulation of the cells in the G1 phase and a later increase in G2/M phase; the pattern of DNA fragmentation obsd. in TEMPOL-treated cells points to an apoptotic mode of cell death. In conclusion, our data suggest that, while the possible cytotoxic effects of TEMPOL should not be overlooked when using this compd. as a biophys. probe or antioxidant, these same properties could be exploited as a novel approach to **cancer** chemotherapy, esp. in **tumor** cells exhibiting unfavorable characteristics, such as a multidrug-resistant phenotype or loss of hormone receptors.

ACCESSION NUMBER: 1997:258309 CAPLUS
DOCUMENT NUMBER: 126:290156
TITLE: Evaluation of tempol radioprotection in a murine **tumor** model
AUTHOR(S): Hahn, Stephen M.; Sullivan, Francis J.; DeLuca, Anne Marie; Krishna, C. Murali; Wersto, Nancy; Venzon, David; Russo, Angelo; Mitchell, James B.
CORPORATE SOURCE: Radiation Biol. Branch, Natl. Cancer Inst., Bethesda, MD, USA
SOURCE: Free Radical Biology & Medicine (1997), 22(7), 1211-1216
CODEN: FRBMEH; ISSN: 0891-5849
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tempol, a stable **nitroxide** free radical compd., is an in vitro and in vivo radioprotector. Previous studies have shown that Tempol protects C3H mice against whole-body radiation-induced bone marrow failure. In this study, the radioprotection of **tumor** tissue was evaluated. RIF-1 **tumor** cells were implanted in female C3H mice 10 d prior to radiation. Groups of mice were injected i.p. with Tempol (275 mg/kg) or PBS followed 10 min later by a single dose of radiation to the **tumor** bed. **Tumor** growth curves generated after 10 and 33.3 Gy doses of radiation showed no difference in growth between the Tempol- and PBS-treated animals. A full radiation dose-response expt. revealed a **tumor** control dose in 50% of the animals in 30 d(TCD50/30) value of 36.7 Gy for Tempol-treated mice and 41.8 Gy for saline-treated mice suggesting no protection of the RIF-1 **tumor** by Tempol. **Tumor** pharmacokinetics were done to det. why Tempol differentially protected bone marrow and not **tumor** cells. Differential redn. of Tempol in the RIF-1 **tumor** and bone marrow was evaluated with EPR spectroscopy 10, 20, and 30 min after injection. Bioredn. of Tempol to its corresponding hydroxylamine (which is not a radioprotector) occurred to a greater extent in RIF-1 **tumor** cells compared to bone marrow. We conclude that the differences in radioprotection may result from enhanced intratumor bioredn. of Tempol to its nonradioprotective hydroxylamine analog. The **nitroxides** as a class of compds. may provide a means to exploit the redox differences between normal tissues and **tumors**.

ACCESSION NUMBER: 1995:979402 CAPLUS
DOCUMENT NUMBER: 124:83285
TITLE: New directions for free radical **cancer** research and medical applications
AUTHOR(S): Hahn, Stephen M.; Krishna, C. Murali; Mitchell, James B.
CORPORATE SOURCE: National Cancer Institute, National Institutes Health, Bethesda, MD, 20892, USA
SOURCE: Advances in Experimental Medicine and Biology (1994), 366(Free Radicals in Diagnostic Medicine), 241-51
CODEN: AEMBAP; ISSN: 0065-2598
PUBLISHER: Plenum
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 36 refs. The development of a class of anti-oxidant compds., the **nitroxides**, which highlight many of the features of free radicals as they pertain to **cancer** research is described.

L5 ANSWER 12 OF 91 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:183461 CAPLUS
DOCUMENT NUMBER: 126:235473
TITLE: The influence of hyperthermia on bioreduction of **nitroxides** by B16 melanoma as studied by in vitro and in vivo ESR
AUTHOR(S): Elas, Martyna; Cieszka, Krystyna; Matuszak, Zenon; Lukiewicz, Stanislaw
CORPORATE SOURCE: Laboratory for Radiobiology and Radiospectroscopy of Cancer, Institute of Molecular Biology, Jagiellonian University, Krakow, Pol.
SOURCE: Current Topics in Biophysics (1996), 20(1), 53-57
CODEN: CTOBEU; ISSN: 1232-9630
PUBLISHER: Wydawnictwo Protext
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Heating either B16 melanoma cells or **tumors** growing in murine tails caused a decrease in the rate of **nitroxide** (NFR) redn. by about 40%. This effect did not last long in **tumors**. Two hours after hyperthermia the rate of redn. returned to the value obsd. in untreated **tumors**. Exposure to hyperthermia resulted in the decline of cellular oxygen consumption by about 30%, but the growth rate of the same cells in culture was not affected. These results indicate that hyperthermia belongs to the factors capable of modifying to a substantial degree the redox state of B16 melanoma cells under in vitro conditions and in situ growing **tumors**.

ACCESSION NUMBER: 1994:652484 CAPLUS
DOCUMENT NUMBER: 121:252484
TITLE: Reduction of lipid-soluble **nitroxides** in CHO cells and macrophage **tumor** cells
AUTHOR(S): Suzuki-Nishimura, Tamiko; Swartz, Harold M.
CORPORATE SOURCE: Dartmouth Medical School, Hanover, NH, USA
SOURCE: Free Radical Biol. Med. (1994), 17(5), 473-9
CODEN: FRBMEH; ISSN: 0891-5849
DOCUMENT TYPE: Journal
LANGUAGE: English

AB There is a need to understand the metab. of **nitroxides** because of their usefulness in measurements in living cells of complex phenomena, such as biophys. properties, redox metab., and the concn. of oxygen at specific sites. As part of a systematic study of the metab. of **nitroxides** in cells, the authors studied Chinese hamster ovary (CHO) cells and mouse macrophage **tumor** (M5076) cells, using a set of lipophilic **nitroxides** based on 5 doxyl stearate: the free acid, the Me ester of the acid, and a phosphatidylcholine with two doxyl stearates esterified to the glycerol. The rates of metab. of these **nitroxides** under anoxia differed significantly as a function of both the type of cell and the type of **nitroxide**. The rates of redn. of the three lipophilic **nitroxides** depended on their localization. The rates of redn. were first order for all three lipophilic **nitroxides**, and the only products detected were the resp. hydroxylamines. Effects of freeze-thawing and incubation temp. differed in the two cell lines. The authors conclude that the metab. of **nitroxides** in different cell lines can be quite different. This may be esp. important in understanding studies using **nitroxides** in living cells, functional organs, and in vivo.

5 ANSWER 8 OF 91 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:492857 CAPLUS
DOCUMENT NUMBER: 129:211678
TITLE: **Nitroxides** tempol and tempo induce divergent signal transduction pathways in MDA-MB 231 breast **cancer** cells
AUTHOR(S): Suy, Simeng; Mitchell, James B.; Ehleiter, Desiree; Haimovitz-Friedman, Adriana; Kasid, Usha
CORPORATE SOURCE: Departments of Radiation Medicine and Biochemistry and Molecular Biology, Lombardi Cancer Center, Georgetown University Medical Center, Washington, DC, 20007, USA
SOURCE: Journal of Biological Chemistry (1998), 273(28), 17871-17878
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tempol and tempo are stable free radical **nitroxides** that possess antioxidant properties. In this study, the authors examd. the effects of these compds. on components of the mitogen-activated protein kinase signal transduction cascade. Tempo treatment (15 min) of MDA-MB 231 human breast **cancer** cells resulted in significant levels of tyrosine phosphorylation of several as yet unidentified proteins compared with equimolar concn. of tempol (10 mM). Both compds. caused tyrosine phosphorylation and activation of Raf-1 protein kinase (30 min, 2-3-fold). Interestingly, however, only tempol caused increased extracellular signal-regulated kinase 1 activity (2 h, .apprx.3-fold). Tempo, but not tempol, potently activated stress-activated protein kinase (2 h, >3-fold). Consistent with these data, tempol was noncytotoxic, whereas tempo induced apoptotic cell death (2 h, >50%). Tempo treatment also resulted in significant elevation of ceramide levels at 30 min (54% over control) and 1 h (71% over control) posttreatment, preceding stress-activated protein kinase activation and apoptosis. These data suggest that in the absence of an environmental oxidative stress, tempol and tempo elicit distinct cellular signaling pathways. The recognition of the mol. mechanisms of **nitroxide** action may have important implications for biol. effectiveness of these compds.

ACCESSION NUMBER: 1982:519982 CAPLUS
DOCUMENT NUMBER: 97:119982
TITLE: Application of **nitroxide** free radicals in **cancer** chemotherapy
AUTHOR(S): Subczynski, Witold K.
CORPORATE SOURCE: Inst. Biol. Mol., Uniw. Jagiellonski, Krakow, 31-001, Pol.
SOURCE: Zesz. Nauk. Uniw. Jagiellon., Pr. Biol. Mol. (1981), 8, 231-7
CODEN: ZNUMDV
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Polish
AB A review with 18 refs.

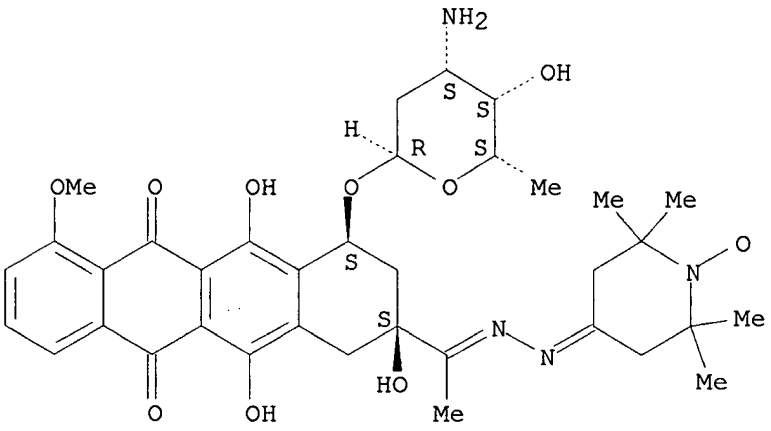
ACCESSION NUMBER: 1997:183462 CAPLUS
DOCUMENT NUMBER: 126:235474
TITLE: In vivo ESR studies on the effect of O2 on bioreduction of **nitroxides** in murine **tumors**
AUTHOR(S): Cieszka, Krystyna; Elas, Martyna; Matuszak, Zenon; Lukiewicz, Stanislaw
CORPORATE SOURCE: Laboratory for Radiobiology and Radiospectroscopy of Cancer, Institute of Molecular Biology, Jagiellonian University, Krakow, Pol.
SOURCE: Current Topics in Biophysics (1996), 20(1), 58-61
CODEN: CTOBEU; ISSN: 1232-9630
PUBLISHER: Wydawnictwo Protext
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The redox state of B16 melanoma **tumors**, evaluated by measuring the rate of redn. of **nitroxides** was studied in vivo and ex vivo under normoxia and hyperoxia. Oxygen was supplied either by intratumoral injection of oxygen-satd. **nitroxide** soln., or by inhalation of O2 mixed with a few percent of air, under in vivo conditions. The decrease in the rate of **nitroxide** free radicals (NFR) redn. by B16 melanoma **tumors** was obsd. both in vivo and ex vivo, after oxygen delivery, whereas this effect was almost absent in normal tissue. The decrease in the rate of NFR redn. varied for different **nitroxides** and was 30 to 70% of the control rate. Both ways of oxygen supply were effective in diminishing the redn. rate of the NFRs. These findings demonstrated the feasibility of influencing the oxygen level in B16 **tumors** and of modifying the redox state of **tumors** in this way.

L5 ANSWER 1 OF 91 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:183463 CAPLUS
DOCUMENT NUMBER: 126:248459
TITLE: Bioreduction of **nitroxides** in murine **tumors** with blocked thiols in the light of the in vivo ESR data
AUTHOR(S): Elas, Martyna; Cieszka, Krystyna; Matuszak, Zenon; Lukiewicz, Stanislaw
CORPORATE SOURCE: Laboratory for Radiobiology and Radiospectroscopy of Cancer, Institute of Molecular Biology, Jagiellonian University, Krakow, Pol.
SOURCE: Current Topics in Biophysics (1996), 20(1), 62-66
CODEN: CTOBEU; ISSN: 1232-9630
PUBLISHER: Wydawnictwo Protext
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Treatment with sulfhydryl blockers caused a decrease in the rate of **nitroxide** free radical (NFR) redn. in melanoma cells under in vitro conditions and in neoplastic tissue in vivo. The tested blockers, Diamide (diazene dicarboxylic acid 1,1-azobis-N,N-dimethylamide) and DEM (di-Et maleate), were equally effective in B16 cells in vitro, whereas in B16 **tumors** growing in situ DEM was more efficient. It was demonstrated that it is possible to alter the redox state of both cells and **tumors** by modifying the level of cellular thiols.

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN **84412-94-2** REGISTRY
CN 1-Piperidinyloxy, 4-[[1-[(2S,4S)-4-[(3-amino-2,3,6-trideoxy-.alpha.-L-lyxo-hexopyranosyl)oxy]-1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-2-naphthacenyl]ethylidene]hydrazono]-2,2,6,6-tetramethyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1-Piperidinyloxy, 4-[[1-[4-[(3-amino-2,3,6-trideoxy-.alpha.-L-lyxo-hexopyranosyl)oxy]-1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-2-naphthacenyl]ethylidene]hydrazono]-2,2,6,6-tetramethyl-, (2S-cis)-
OTHER NAMES:
CN Emoxyl
CN Ruboxyl
CN Ruboxyl 1
FS STEREOSEARCH
DR 83138-78-7
MF C36 H45 N4 O10
CI COM
LC STN Files: BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, DDFU, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, RTECS*, TOXCENTER
(*File contains numerically searchable property data)

Absolute stereochemistry.
Double bond geometry unknown.



32 REFERENCES IN FILE CA (1967 TO DATE)
33 REFERENCES IN FILE CAPLUS (1967 TO DATE)

ANSWER 15 OF 93 TOXLINE
ACCESSION NUMBER: 1999:49654 TOXLINE
DOCUMENT NUMBER: CRISP-99-CA79378-01
TITLE: PNA, NITROXIDE AND 6OHDA FOR METASTATIC NEUROBLASTOMA.
AUTHOR: HSIA C J
CORPORATE SOURCE: SYNZYME TECHNOLOGIES INC, ONE TECHNOLOGY DRIVE, SUITE E-, IRVINE, CA 92618
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, NATIONAL CANCER INSTITUTE.
CONTRACT NUMBER: 1R43CA79378-01
SOURCE: (1998). Crisp Data Base National Institutes Of Health. Award Type: G = Grant
PUB. COUNTRY: United States
DOCUMENT TYPE: (RESEARCH)
FILE SEGMENT: CRISP
LANGUAGE: English
ENTRY MONTH: 199904
AB RPROJ/CRISP Despite current therapies, the prognosis in metastatic neuroblastoma remains dismal. An experimental chemotherapeutic agent for this **tumor** is the cytotoxic neurotransmitter analog 6-hydroxyl-dopamine (6OHDA). This compound, generates cytolytic oxygen radicals, and is preferentially taken up by the **tumor**; predictably, though, there is significant systemic 6OHDA toxicity. In an attempt to limit systemic toxicity, 6OHDA has been tested in conjunction with the antioxidant nitroxide compound **TEMPOL**; this substantially improves the therapeutic index of 6OHDA. However, **TEMPOL** has a short half-life in vivo, making it necessary to administer **TEMPOL** dosages approaching the level of **TEMPOL** toxicity. The present Phase I proposal focuses on a novel compound, polynitroxyl albumin (PNA), which can reduce **TEMPOL** toxicity by prolonging the active half-life of **TEMPOL** in vivo and allowing lower **TEMPOL** dosages to be used. (The project will test the three- component System of 6OHDA, **TEMPOL**, and PNA in a mouse model of neuroblastoma. The specific aim is to determine whether PNA can safely maintain **TEMPOL** levels capable of limiting systemic 6OHDA toxicity, while allowing 6OHDA to kill **tumor** cells efficiently. Based on a successful Phase I project, Phase II will involve progression to a clinical trial. PROPOSED COMMERCIAL APPLICATIONS: If successful this research program will result in improved medical treatment of metastatic neuroblastoma. The ability to improve outcomes in this childhood disease would provide important human and health care benefits and represent a significant commercial opportunity.

L4 ANSWER 16 OF 93 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 7
ACCESSION NUMBER: 1998:774234 CAPLUS
DOCUMENT NUMBER: 130:29069
TITLE: Use of **Tempol** in the prevention of photoaging
INVENTOR(S): Bernstein, Eric
PATENT ASSIGNEE(S): Thomas Jefferson University, USA
SOURCE: U.S., 5 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5840734	A	19981124	US 1997-851739	19970506

AB A method of preventing photoaging and other types of sun damage by topically applying a compn. contg. **Tempol** is provided. Pharmaceutical compns. comprising **Tempol** for the prevention of photoaging and other types of sun damage are also provided. Homozygous line of transgenic mice expressing the 5.2-kb human elastin promoter linked to a chloramphenicol acetyltransferase (CAT) reporter gene was used. **Tempol** reduced the CAT activity significantly.

REFERENCE COUNT: 18

REFERENCE(S):

(2) Bissett; Photodermatol Photoimmunol Photomed 1990, V7, P56 CAPLUS

(3) Chen; J Invest Dermatol 1986, V87, P334 CAPLUS

(5) Emerit; 1992 CAPLUS

(6) Frances, C; Int J Dermatol 1984, V23, P166 CAPLUS

(7) Goffman; Int J Rad Onc Bio Phys 1992, V22, P803 CAPLUS

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17 OF 93 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:800011 CAPLUS
DOCUMENT NUMBER: 130:20564
TITLE: The use of a nitroxide or a prodrug thereof in the prophylactic and therapeutic treatment of **cancer**
INVENTOR(S): Mitchell, James B.; Russo, Angelo; Deluca, Anne Marie; Cherukuri, Murali Krishna
PATENT ASSIGNEE(S): United States Dept. of Health and Human Services, USA
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9853835	A1	19981203	WO 1998-US10685	19980527
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9875987	A1	19981230	AU 1998-75987	19980527
EP 986393	A1	20000322	EP 1998-923772	19980527
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRIORITY APPLN. INFO.:			US 1997-47724	19970527
			WO 1998-US10685	19980527

OTHER SOURCE(S): MARPAT 130:20564
AB A method is provided for the prophylactic and therapeutic treatment of **cancer**. The method comprises administering to an animal, preferably a mammal, more preferably a human, at risk for developing a **cancer** or having a **cancer** a nitroxide or a prodrug thereof, wherein the nitroxide or prodrug thereof, preferably alicyclic or heterocyclic (Markush included), in an amt. sufficient to prevent or treat the **cancer**, wherein the **cancer** is susceptible to prevention or treatment by the nitroxide or prodrug thereof. Also provided is a compn. for use in the method.
REFERENCE COUNT: 4
REFERENCE(S): (1) Monti; PAACR ANNUAL MEETING 1977, V38(0), P193
(2) Monti; PAACR ANNUAL MEETING 1995, V36(0), P387
(3) Monti; PAACR ANNUAL MEETING 1998, V39(0), P90
(4) Us Government; WO 9640127 A 1996 CAPLUS

L4 ANSWER 18 OF 93 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:169475 CAPLUS
DOCUMENT NUMBER: 128:248580
TITLE: Association of NO synthase inhibitors with trappers of reactive oxygen species
INVENTOR(S): Chabrier De Lassauniere, Pierre-Etienne; Bigg, Denis

PATENT ASSIGNEE(S): Societe De Conseils De Recherches Et D'applications Scientifiques (S.C.R.A.S, Fr.; Chabrier De Lassauniere, Pierre-Etienne; Bigg, Denis

SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9809653	A1	19980312	WO 1997-FR1567	19970905
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
FR 2753098	A1	19980313	FR 1996-10875	19960906
FR 2753098	B1	19981127		
AU 9742111	A1	19980326	AU 1997-42111	19970905
EP 939654	A1	19990908	EP 1997-940183	19970905
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000517336	T2	20001226	JP 1998-512314	19970905
NO 9901100	A	19990505	NO 1999-1100	19990305
PRIORITY APPLN. INFO.:			FR 1996-10875	19960906
			WO 1997-FR1567	19970905

AB The invention concerns a pharmaceutical compn. contg., as active principle, at least one NO synthase-inhibiting substance and at least one reactive oxygen-trapping substance, optionally with a pharmaceutically acceptable support. The invention also concerns a product contg. at least one NO synthase-inhibiting substance and at least one reactive oxygen-trapping substance as combined product of these active principles in sep. form.

L4 ANSWER 19 OF 93 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 1998316364 MEDLINE
DOCUMENT NUMBER: 98316364
TITLE: Nitroxides **tempol** and tempo induce divergent signal transduction pathways in MDA-MB 231 breast **cancer** cells.
AUTHOR: Suy S; Mitchell J B; Ehleiter D; Haimovitz-Friedman A; Kasid U
CORPORATE SOURCE: Departments of Radiation Medicine and Biochemistry and Molecular Biology, Lombardi Cancer Center, Georgetown University Medical Center, Washington D.C. 20007, USA.
CONTRACT NUMBER: CA58984 (NCI)
CA68322/OD68322 (NCI)
CA74175 (NCI)
+
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Jul 10) 273 (28) 17871-8.
Journal code: HIV. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199810
ENTRY WEEK: 19981002
AB **Tempol** and tempo are stable free radical nitroxides that possess

antioxidant properties. In this study, we examined the effects of these compounds on components of the mitogen-activated protein kinase signal transduction cascade. Tempo treatment (15 min) of MDA-MB 231 human breast **cancer** cells resulted in significant levels of tyrosine phosphorylation of several as yet unidentified proteins compared with equimolar concentration of **tempol** (10 mM). Both compounds caused tyrosine phosphorylation and activation of Raf-1 protein kinase (30 min, 2-3-fold). Interestingly, however, only **tempol** caused increased extracellular signal-regulated kinase 1 activity (2 h, approximately 3-fold). On the other hand, tempo, but not **tempol**, potently activated stress-activated protein kinase (2 h, >3-fold). Consistent with these data, **tempol** was found to be noncytotoxic, whereas tempo induced apoptotic cell death (2 h, >50%). Tempo treatment also resulted in
significant elevation of ceramide levels at 30 min (54% over control) and 1 h (71% over control) posttreatment, preceding stress-activated protein kinase activation and apoptosis. These data suggest that in the absence of
an environmental oxidative stress, **tempol** and tempo elicit distinct cellular signaling pathways. The recognition of the molecular mechanisms of nitroxide action may have important implications for biological effectiveness of these compounds.

L4 ANSWER 20 OF 93 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 1998268617 MEDLINE
DOCUMENT NUMBER: 98268617
TITLE: Antiproliferative effect of the piperidine nitroxide **TEMPOL** on neoplastic and nonneoplastic mammalian cell lines.
AUTHOR: Gariboldi M B; Lucchi S; Caserini C; Supino R; Oliva C; Monti E
CORPORATE SOURCE: Applied Pharmacology Section, Institute of Pharmacology, University of Milan, Italy.
SOURCE: FREE RADICAL BIOLOGY AND MEDICINE, (1998 Apr) 24 (6) 913-23.
Journal code: FRE. ISSN: 0891-5849.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY WEEK: 19990104

AB The stable nitroxide 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl (**TEMPOL**) is widely used as a probe in biophysical studies and as an antioxidant in several experimental models. The potential cytotoxic effects of **TEMPOL** were tested on a panel of human and rodent cell lines, and the nitroxide proved to be significantly more effective in
inhibiting the growth of neoplastic than nonneoplastic cell lines after a 96-h exposure. More detailed studies on MCF-7/WT cells indicate that at least 24 h are necessary for **TEMPOL** to induce irreversible cell damage, which seems to be related to the reactivity of the nitroxyl group.
This observation, together with the antagonistic effect of N-acetylcysteine, suggests an involvement of free radical-mediated processes. Cell cycle studies indicate a biphasic effect of **TEMPOL**, with a short-term accumulation of the cells in the G1 phase and a later increase in G2/M phase; the pattern of DNA fragmentation observed in **TEMPOL**-treated cells points to an apoptotic mode of cell death. In conclusion, our data suggest that, while the possible cytotoxic effects of
TEMPOL should not be overlooked when using this compound as a biophysical probe or antioxidant, these same properties could be exploited
as a novel approach to **cancer** chemotherapy, especially in

tumor cells exhibiting unfavorable characteristics, such as a multidrug-resistant phenotype or loss of hormone receptors.

L4 ANSWER 21 OF 93 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 1999059231 MEDLINE
DOCUMENT NUMBER: 99059231
TITLE: Redox generation of nitric oxide to radiosensitize hypoxic cells.
AUTHOR: Mitchell J B; DeGraff W; Kim S; Cook J A; Gamson J; Christodoulou D; Feelisch M; Wink D A
CORPORATE SOURCE: Radiation Biology Branch, National Cancer Institute, Bethesda, MD 20892, USA.
SOURCE: INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY, BIOLOGY, PHYSICS, (1998 Nov 1) 42 (4) 795-8.
Journal code: G97. ISSN: 0360-3016.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199902
ENTRY WEEK: 19990204
AB PURPOSE: Previous studies have shown that nitric oxide (NO) delivered from NO donor agents sensitizes hypoxic cells to ionizing radiation. In the present study, nitroxyl (NO-), a potential precursor to endogenous NO production, was evaluated for hypoxic cell radiosensitization, either alone or in combination with electron acceptor agents. METHODS AND MATERIALS: Radiation survival curves of Chinese hamster V79 lung fibroblasts under aerobic and hypoxic conditions were assessed by clonogenic assay. Hypoxia induction was achieved by metabolism-mediated oxygen depletion in dense cell suspensions. Cells were treated with NO- produced from the nitroxyl donor Angeli's salt (AS, Na2N2O3, sodium trioxodinitrate), in the absence or presence of electron acceptor agents, ferricyanide, or **tempol**. NO concentrations resulting from the combination of AS and ferricyanide or **tempol** were measured under hypoxic conditions using an NO-sensitive electrode. RESULTS: Treatment of V79 cells under hypoxic conditions with AS alone did not result in radiosensitization; however, the combination of AS with ferricyanide or **tempol** resulted in significant hypoxic radiosensitization with SERs of 2.5 and 2.1, respectively. Neither AS alone nor AS in combination with ferricyanide or **tempol** influenced aerobic radiosensitivity. The presence of NO generated under hypoxic conditions from the combination of AS with ferricyanide or **tempol** was confirmed using an NO-sensitive electrode. CONCLUSION: Combining NO- generated from AS with electron acceptors results in NO generation and substantial hypoxic cell radiosensitization. NO- derived from donor agents or endogenously produced in **tumors**, combined with electron acceptors, may provide an important strategy for radiosensitizing hypoxic cells and warrants in vivo evaluation.

L4 ANSWER 22 OF 93 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998352595 EMBASE
TITLE: A practitioner's guide to **cancer**-related alopecia.
AUTHOR: Dorr V.J.
CORPORATE SOURCE: Dr. V.J. Dorr, Ellis Fischel Cancer Center, University of Missouri, 115 Business Loop 70 W, Columbia, MO 65203, United States
SOURCE: Seminars in Oncology, (1998) 25/5 (562-570).
Refs: 67
ISSN: 0093-7754 CODEN: SOLGAV
COUNTRY: United States

DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 013 Dermatology and Venereology
016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Alopecia due to the side effects of the treatment of **cancer** is one of the most common and emotionally troublesome effects of **cancer** therapy. Preventive measures, primarily scalp hypothermia, can be effective in some cases, but the worry of subsequent scalp metastasis remains. Investigative studies in animals are hindered by a poor animal alopecia model. Several promising agents require translation into clinical practice. Until then, disguising the alopecia with wigs, hats, or turbans remains the mainstay of treatment.

L4 ANSWER 23 OF 93 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998224202 EMBASE
TITLE: Normal tissue protection in **cancer** therapy - Progress and prospects.
AUTHOR: Devi P.U.
CORPORATE SOURCE: Dr. P.U. Devi, Department of Radiobiology, Kasturba Medical
College, Manipal 576 119, India
SOURCE: Acta Oncologica, (1998) 37/3 (247-252).
Refs: 45
ISSN: 0284-186X CODEN: ACTOEL
COUNTRY: Norway
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Normal tissue tolerance is a major dose-limiting factor in radiotherapy and chemotherapy of **cancer**. During the past few decades several investigations have been directed toward increasing normal tissue tolerance by using chemical protectors against radiation and drug toxicity. WR-2721, the phosphorylated aminothiol, synthesized in the 1960s, has been hailed as the best chemical protector discovered so far. But its systemic toxicity after repeated administration in **cancer** patients during clinical trials has been a deterrent against its acceptance in routine radiotherapy, though more encouraging results have been reported with chemotherapy. The 1980s found a surge of activity in the field of chemical protection research, which has resulted in the discovery of many non-thiol protectors, particularly the biological response modifiers and antioxidants. It has also been found that protection by WR-2721 can be improved and its toxicity reduced by combination with some low potent protective chemicals. This review analyzes the major reports on chemical protectors published during the past ten years.

L4 ANSWER 24 OF 93 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 1998196935 MEDLINE
DOCUMENT NUMBER: 98196935
TITLE: Slow rate of free radical scavenging in the gastric antral mucosa of male Wistar rats: a possible mechanism of gastric
carcinogenesis induced by N-methyl-N'-nitro-N-nitrosoguanidine.
AUTHOR: Mikuni T; Tatsuta M
CORPORATE SOURCE: Department of Gastrointestinal Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Japan.

SOURCE: INTERNATIONAL JOURNAL OF CANCER, (1998 Apr 13) 76 (2) 228-31.
Journal code: GQU. ISSN: 0020-7136.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199806
ENTRY WEEK: 19980603

AB We previously suggested that hydroxyl free radical (-OH) production may play a role in carcinogenesis induced by N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). MNNG-induced gastric **cancer** in rats and human gastric carcinoma occur most often in the antral mucosa and rarely in the normal fundic mucosa. We hypothesized that regional differences in anti-oxidant activity may be responsible. In the present study, we examined anti-oxidant activity by comparing the relative rates of reduction of a nitroxide free radical, 4-hydroxy-2,2,6,6-tetramethyl-1-piperidinyloxy (**Tempol**), in the antral and fundic mucosa of male Wistar rats using ESR. The relative rate of **Tempol** reduction was significantly slower in the antral portion of the wall than in the fundic portion when **Tempol** [4 x 10(-6) mole/mg wet weight of gastric wall] in HEPES buffer (pH 7.4) was spread over the mucosal surface of a section of the gastric wall. Addition of a sulfhydryl group modulator, N-ethylmaleimide, to the mucosal surface before treatment with **Tempol** removed the significant difference observed in the rates of reduction in the antral and fundic portions of the gastric wall. No signals were detected in the muscle layer. Our results indicate that the relative rate of free radical reduction by sulfhydryl groups was significantly slower in the antral mucosa than in the fundic mucosa. We therefore conclude that a regional difference in the rates of reduction of free radicals by sulfhydryl groups may result in the site susceptible to development of MNNG-induced gastric **cancer**.

L4 ANSWER 25 OF 93 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 1999125764 MEDLINE
DOCUMENT NUMBER: 99125764
TITLE: Phosphine-induced oxidative stress in Hepa 1c1c7 cells.
AUTHOR: Hsu C H; Quistad G B; Casida J E
CORPORATE SOURCE: Department of Environmental Science, Policy and Management,
University of California, Berkeley 94720-3112, USA.
CONTRACT NUMBER: P01 ES00049 (NIEHS)
R01 ES08762 (NIEHS)
SOURCE: TOXICOLOGICAL SCIENCES, (1998 Nov) 46 (1) 204-10.
Journal code: CZ1. ISSN: 1096-6080.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199907
ENTRY WEEK: 19990702

AB Phosphine (PH3), from hydrolysis of metal phosphides, is an important insecticide (aluminum phosphide) and rodenticide (zinc phosphide) and is considered genotoxic and cytotoxic in mammals. This study tests the hypothesis that PH3-induced genotoxicity and cytotoxicity are associated with oxidative stress by examining liver (Hepa 1c1c7) cells for possible relationships among cell death, increases in reactive oxygen species (ROS) and lipid peroxidation, and elevated 8-hydroxyguanine (8-OH-Gua) in DNA. PH3 was generated from 0.5 mM magnesium phosphide (Mg3P2) to give 1 mM PH3 as the nominal and maximal concentration. This level causes 31% cell death at 6 h, measured by lactate dehydrogenase leakage, with appropriate

dependence on concentration and time. The intracellular ROS level is elevated within 0.5 h following exposure to PH3, peaking at 235% of the control by about 1 h. Lipid peroxidation (measured as malondialdehyde plus 4-hydroxyalkenals) is increased up to 504% by PH3 at 6 h in a time-dependent manner. The level of 8-OH-Gua in DNA, a biomarker of mutagenic oxidative DNA damage analyzed by GC/MS, increases to 259% at 6 h after PH3 treatment. Antioxidants significantly attenuate the PH3-induced ROS formation, lipid peroxidation, 8-OH-Gua formation in DNA, and cell death, with the general order for effectiveness of GSH (5 mM) and D-mannitol (10 mM) (hydroxyl radical scavengers), then **Tempol** (2.5 mM) and sodium azide (3 mM) (superoxide anion and singlet oxygen scavengers, respectively). These studies support the hypothesis that PH3-induced mutagenic and cytotoxic effects are due to increased ROS levels, probably hydroxyl radicals, initiating oxidative damage.

L4 ANSWER 26 OF 93 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:194484 BIOSIS
DOCUMENT NUMBER: PREV199800194484
TITLE: The piperidine nitroxide **TEMPOL** induced apoptosis and p21waf1/cip1 expression in p53-deficient cells.
AUTHOR(S): Monti, E. (1); Gariboldi, M. B.; Grossi, S.; Lucchi, S.; Supino, R.
CORPORATE SOURCE: (1) Ist. Pharmacol., Univ. Milan, 120129 Milan Italy
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 1998) Vol. 39, pp. 90. Meeting Info.: 89th Annual Meeting of the American Association for Cancer Research New Orleans, Louisiana, USA March 28-April 1, 1998 American Association for Cancer Research . ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 27 OF 93 TOXLINE
ACCESSION NUMBER: 1998:61459 TOXLINE
DOCUMENT NUMBER: CRISP-98-SC06387-10
TITLE: NITROXIDES AS PROTECTORS AGAINST OXIDATIVE STRESS.
AUTHOR: MITCHELL J B
CORPORATE SOURCE: NCI, NIH
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, DIVISION OF CLINICAL SCIENCES - NCI.
CONTRACT NUMBER: 1Z01SC06387-10
SOURCE: (1997). Crisp Data Base National Institutes Of Health. Award Type: A = Intramural Project
DOCUMENT TYPE: (RESEARCH)
FILE SEGMENT: CRISP
LANGUAGE: English
ENTRY MONTH: 199805
AB RPROJ/CRISP Nitroxides (such as **tempol**) which have been used as EPR spin labels have been shown to exhibit superoxide dismutase (SOD) activity and are quite effective agents in protecting cells against a wide variety of oxidative stresses including hydrogen peroxide, superoxide, organic hydroperoxides, redox-cycling chemotherapy drugs, and ionizing radiation. We have demonstrated that **Tempol** protects both cells in vitro and mice against ionizing radiation. Thus, the nitroxides represent a new class of radiation protectors that may have widespread use in protecting humans against radiation. Importantly, we have shown that **tempol** does not protect rodent **tumor** tissue; the

mechanism of which we believe involves differential metabolic reduction properties of normal versus **tumor** tissue. In vivo electron paramagnetic resonance imaging studies in a **tumor**-bearing animal model has shown more rapid reduction of nitroxides in **tumor** compared to normal tissue. We have completed an in vitro study to identify the most efficient nitroxide for protection purposes. Over 110 nitroxides were evaluated in a structure activity relationship study. We have identified 6 nitroxides that afford significantly more radioprotection than **tempol** (the first nitroxide shown to have radioprotective properties) and have also identified 3 analogs that radiosensitize aerobic cells. These agents will be evaluated and compared with **tempol** in vivo. Large quantities of several of the six protective nitroxides are being synthesized for further study of these newly discovered protectors. We have recently shown that heme proteins exposed to oxidants form highly toxic ferryl moieties and that nitroxides detoxify these toxic species and confer enhanced catalase-like activity to heme species. Reasoning in an analogous fashion we are investigating the affects of nitroxides as modulators of nitric oxide synthase because intermediates within the enzyme which depend on heme redox chemistry may be altered in the presence of nitroxides. We are also investigating in in vivo models, the activity of nitroxides appended to macromolecules such as albumin. Since these agents readily penetrate cell membranes, they may be of use in other areas of medical research such as ischemia/reperfusion injury studies, prevention of cataracts, inflammatory processes and aging.

L4 ANSWER 28 OF 93 CANCERLIT
ACCESSION NUMBER: 1998638298 CANCERLIT
DOCUMENT NUMBER: 98638298
TITLE: DNA damage and apoptosis in human leukemic cells treated with the piperidine nitroxide **TEMPOL** (Meeting abstract).
AUTHOR: Monti E; Gariboldi M B; Supino R; Piccinini F
CORPORATE SOURCE: Inst. of Pharmacology, Univ. of Milan, Italy.
SOURCE: Proc Annu Meet Am Assoc Cancer Res, (1997). Vol. 38, pp. A1298.
ISSN: 0197-016X.
DOCUMENT TYPE: (MEETING ABSTRACTS)
FILE SEGMENT: ICDB
LANGUAGE: English
ENTRY MONTH: 199806

AB Piperidine nitroxide radicals act as antioxidants in several free radical-mediated pathologies (Krishna and Samuni, Methods Enzymol 234:580, 1994). A recent study showed that these compounds are mutagenic as well as cytotoxic against DNA repair-deficient bacterial strains (Wang et al, Biochim Biophys Acta 1305:71, 1996). This observation suggested that similar effects might be elicited in **tumor** cell lines. In the present study we evaluated the cytotoxicity of 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl (**TEMPOL**) against two human leukemic cell lines, HL-60 and KG1. Our results show that HL-60 cells are more sensitive than KG1 (IC50 0.35 +/- 0.08 mM and 1.3 +/- 0.14 mM, respectively for 96-h exposure, M +/- SE). Analysis of DNA fragmentation by agarose gel electrophoresis and filter binding assay in **TEMPOL** -treated HL-60 cells showed a dose-dependent effect, which was absent in KG1 cells. The two cell lines exhibited different cell cycle distributions following **TEMPOL** treatment, with a partial G1 block for KG1 and a shift towards S and G2/M phases for HL-60. Cell cycle studies also evidenced a dose and time-dependent increase of apoptosis for HL-60 but

not for KG1 cells. Immunoblot analysis of bcl-2 indicated the presence of higher protein levels in KG1 than in HL-60 cells. We conclude that cytotoxic effect of **TEMPOL** in human leukemic cells is related to induction of apoptosis.

L4 ANSWER 29 OF 93 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 97252526 MEDLINE
DOCUMENT NUMBER: 97252526
TITLE: Evaluation of **tempol** radioprotection in a murine **tumor** model.
AUTHOR: Hahn S M; Sullivan F J; DeLuca A M; Krishna C M; Wersto N; Venzon D; Russo A; Mitchell J B
CORPORATE SOURCE: Radiation Biology Branch, National Cancer Institute, Bethesda, MD 20892, USA.
SOURCE: FREE RADICAL BIOLOGY AND MEDICINE, (1997) 22 (7) 1211-6. Journal code: FRE. ISSN: 0891-5849.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199710
ENTRY WEEK: 19971001
AB **Tempol**, a stable nitroxide free radical compound, is an in vitro and in vivo radioprotector. Previous studies have shown that **Tempol** protects C3H mice against whole-body radiation-induced bone marrow failure. In this study, the radioprotection of **tumor** tissue was evaluated. RIF-1 **tumor** cells were implanted in female C3H mice 10 d prior to radiation. Groups of mice were injected intraperitoneally with **Tempol** (275 mg/kg) or PBS followed 10 min later by a single dose of radiation to the **tumor** bed. **Tumor** growth curves generated after 10 and 33.3 Gy doses of radiation showed no difference in growth between the **Tempol**- and PBS-treated animals. A full radiation dose-response experiment revealed a **tumor** control dose in 50% of the animals in 30 d (TCD(50/30)) value of 36.7 Gy for **Tempol**-treated mice and 41.8 Gy for saline-treated mice suggesting no protection of the RIF-1 **tumor** by **Tempol**. **Tumor** pharmacokinetics were done to determine why **Tempol** differentially protected bone marrow and not **tumor** cells. Differential reduction of **Tempol** in the RIF-1 **tumor** and bone marrow was evaluated with EPR spectroscopy 10, 20, and 30 min after injection. Bioreduction of **Tempol** to its corresponding hydroxylamine (which is not a radioprotector) occurred to a greater extent in RIF-1 **tumor** cells compared to bone marrow. We conclude that the differences in radioprotection may result from enhanced intratumor bioreduction of **Tempol** to its nonradioprotective hydroxylamine analogue. The nitroxides as a class of compounds may provide a means to exploit the redox differences between normal tissues and **tumors**.

L4 ANSWER 30 OF 93 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 1998025416 MEDLINE
DOCUMENT NUMBER: 98025416
TITLE: **Tempol** inhibits neutrophil and hydrogen peroxide-mediated DNA damage.
AUTHOR: Hahn S M; Mitchell J B; Shacter E
CORPORATE SOURCE: Radiation Biology Branch, National Cancer Institute, Bethesda, MD 20892, USA.
SOURCE: FREE RADICAL BIOLOGY AND MEDICINE, (1997) 23 (6) 879-84. Journal code: FRE. ISSN: 0891-5849.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY WEEK: 19980104

AB Inflammatory conditions characterized by neutrophil activation are associated with a variety of chronic diseases. Reactive oxygen species are produced by activated neutrophils and produce DNA damage which may lead to tissue damage. Previous studies have shown that activated murine neutrophils induce DNA strand breaks in a target plasmacytoma cell, RIMPC 2394. We studied the effect of a water soluble nitroxide anti-oxidant, **Tempol**, on murine neutrophil induction of DNA strand breaks in this system. Murine neutrophils were isolated from the peritoneal cavity of BALB/cAn mice after an i.p. injection of pristane oil. Neutrophils were activated by the phorbol ester PMA and co-incubated with RIMPC 2394 cells. Control alkaline elution studies revealed progressive DNA strand breaks in RIMPC cells with time. The addition of **Tempol** to the incubation mixture prevented DNA damage in a dose dependent fashion. Five mM **Tempol** provided complete protection. **Tempol** protection against DNA strand breaks was similar for both stimulated neutrophils and exogenously added hydrogen peroxide. Measurement of hydrogen peroxide produced by stimulated neutrophils demonstrated that **Tempol** did not decrease hydrogen peroxide concentration. Oxidation of reduced metals, thereby interfering with the production of hydroxyl radical, is the most likely mechanism of nitroxide protection, although superoxide dismutase (SOD) like activity and scavenging of carbon-based free radicals may also account for a portion of the observed protection. The anti-oxidant activity of **Tempol** inhibited DNA damage by activated neutrophils. The nitroxides as a class of compounds may have a role in the investigation and modification of inflammatory conditions.

L4 ANSWER 31 OF 93 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER:	97346959 EMBASE
DOCUMENT NUMBER:	1997346959
TITLE:	Toxicity antagonists in **cancer** therapy.
AUTHOR:	Trotti A.
CORPORATE SOURCE:	Dr. A. Trotti, H.L. Moffitt Canc. Center Res. Inst., 12902 Magnolia Drive, Tampa, FL 33612, United States
SOURCE:	Current Opinion in Oncology, (1997) 9/6 (569-578). Refs: 80 ISSN: 1040-8746 CODEN: CUOOE8
COUNTRY:	United States
DOCUMENT TYPE:	Journal; General Review
FILE SEGMENT:	006 Internal Medicine 016 Cancer 025 Hematology 030 Pharmacology 037 Drug Literature Index 038 Adverse Reactions Titles
LANGUAGE:	English
SUMMARY LANGUAGE:	English

AB Modern **cancer** therapy produces substantial acute and chronic toxicity which impairs quality of life and limits the effectiveness of treatment. Recent clinical and laboratory data suggest that repair of treatment-related injury is a multiphase and continuous process providing multiple opportunities for pharmacologic intervention. A host of agents (toxicity antagonists) are under development that modulate normal tissue response or interfere with mechanisms of toxicity. Although significant challenges remain, the routine application of such agents promises to substantially reduce treatment related morbidity and potentially allow treatment intensification in high-risk disease.

L4 ANSWER 32 OF 93 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1997:422746 CAPLUS
DOCUMENT NUMBER: 127:144745
TITLE: New spin labeled analogs of podophyllotoxin as potential antitumor agents
AUTHOR(S): Wang, Yan-guang; Pan, Jian-lin; Shi, Jian-feng; Chen, Yao-zu
CORPORATE SOURCE: Department Chemistry, Zhejiang University, Hangzhou, 310027, Peop. Rep. China
SOURCE: Life Sci. (1997), 61(5), 537-542
CODEN: LIFSAK; ISSN: 0024-3205
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Four new nitroxyl labeled derivs. of podophyllotoxin, 4-(2,2,6,6-tetramethyl-1-oxyl-4-piperidyl)oxy-epipodophyllotoxin, 4-(2,2,6,6-tetramethyl-1-oxyl-4-piperidyl)oxy-4'-demethylepipodophyllotoxin, 4-(2,2,5,5-tetramethyl-1-oxyl-3-pyrrolinyl)formyloxy-epipodophyllotoxin and 4-(2,2,5,5-tetramethyl-1-oxyl-3-pyrrolinyl)formyloxy-4'-demethylepipodophyllotoxin, have been synthesized and evaluated for their antitumor activity in vitro. The 4'-demethyl-epipodophyllotoxins showed superior activity to the clin. used etoposide (VP-16) in their inhibition of leukemia P388, lung **cancer** A549 and stomach carcinoma SGC-7901 cells. The 4'-demethyl-epipodophyllotoxins was more active than the eipodophyllotoxins lacking a free phenolic hydroxyl group at C-4'.

L4 ANSWER 33 OF 93 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:63740 CAPLUS
DOCUMENT NUMBER: 128:200636
TITLE: Hexamethylene bisacetamide (HMBA) effects on ESR spectra of TEMPO labeling in proteins
AUTHOR(S): Xie, Dongxu; Feng, Liangbo; Li, Shuben; Ren, Liqin
CORPORATE SOURCE: Administration Department of Lanzhou General Hospital of Lanzhou Command PLA, Lanzhou, 730050, Peop. Rep. China
SOURCE: Bopuxue Zazhi (1997), 14(6), 527-532
CODEN: BOZAE2; ISSN: 1000-4556
PUBLISHER: Zhongguo Kexueyuan Wuhan Wuli Yanjiuso
DOCUMENT TYPE: Journal
LANGUAGE: English

AB An ESR spectrum of 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxy (TEMPO) labeled on human bladder carcinoma (BIU-87) cells and its fraction was detected for the effect of HMBA which can induce many types of **tumor** cells differentiation toward normal cell. TEMPO mols. might be located inside proteins. Bound TEMPO mols., at least some of them, are reversible at the existence of hexamethylene bisacetamide (HMBA). These results suggest that they must be involved in the direct action on some proteins during HMBA's inducing the differentiation of **tumor** cells.

L4 ANSWER 34 OF 93 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:231500 BIOSIS
DOCUMENT NUMBER: PREV199799530703
TITLE: DNA damage and apoptosis in human leukemic cells treated with the piperidine nitroxide **TEMPOL**.
AUTHOR(S): Monti, E. (1); Gariboldi, M. B.; Supino, R.; Piccinini, F.
CORPORATE SOURCE: (1) Inst. Pharmacology, Univ. Milan, Milan Italy
SOURCE: Proceedings of the American Association for Cancer Research
Annual Meeting, (1997) Vol. 38, No. 0, pp. 193.
Meeting Info.: Eighty-eighth Annual Meeting of the American

Association for Cancer Research San Diego, California, USA
April 12-16, 1997
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; Abstract
LANGUAGE: English

L4 ANSWER 35 OF 93 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:376500 BIOSIS
DOCUMENT NUMBER: PREV199799675703
TITLE: Sunscreens: The way forward: Immune protection factors and protection by oxygen radical scavengers.
AUTHOR(S): Halliday, G. M.; Damian, D. L.; Yuen, K.; Barnetson, R.
CORPORATE SOURCE: Dep. Med., Univ. Sydney, Royal Prince Alfred Hosp., Sydney Australia
SOURCE: Melanoma Research, (1997) Vol. 7, No. SUPPL. 1, pp. S63.
Meeting Info.: 4th World Conference on Melanoma Sydney, Australia June 10-14, 1997
ISSN: 0960-8931.
DOCUMENT TYPE: Conference; Abstract
LANGUAGE: English

L4 ANSWER 36 OF 93 TOXLINE
ACCESSION NUMBER: 1997:62387 TOXLINE
DOCUMENT NUMBER: CRISP-97-SC06387-09
TITLE: NITROXIDES AS PROTECTORS AGAINST OXIDATIVE STRESS.
AUTHOR: RUSSO A
CORPORATE SOURCE: NCI, NIH
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, NATIONAL CANCER INSTITUTE.
CONTRACT NUMBER: 1Z01SC06387-09
SOURCE: (1996). Crisp Data Base National Institutes Of Health.
Award Type: A = Intramural Project
DOCUMENT TYPE: (RESEARCH)
FILE SEGMENT: CRISP
LANGUAGE: English
ENTRY MONTH: 199705
AB RPROJ/CRISP Nitroxides (such as **tempol**) which have been used as EPR spin labels have been shown to exhibit superoxide dismutase (SOD) activity and are quite effective agents in protecting cells against a wide variety of oxidative stresses including hydrogen peroxide, superoxide, organic hydroperoxides, redox-cycling chemotherapy drugs, and ionizing radiation. We have demonstrated that **Tempol** protects both cells in vitro and mice against ionizing radiation. Thus, the nitroxides represent a new class of radiation protectors that may have widespread use in protecting humans against radiation. Importantly, we have shown that **tempol** does not protect rodent **tumor** tissue; the mechanism of which we believe involves differential metabolic reduction properties of normal versus **tumor** tissue. In vivo electron paramagnetic resonance imaging studies in **tumor**-bearing animals are underway to determine if a differential reduction of nitroxides exists between normal and **tumor** tissue. We have completed an in vitro study to identify the most efficient nitroxide for protection purposes. Over 110 nitroxides were evaluated in a structure activity relationship study. We have identified 6 nitroxides that afford significantly more radioprotection than **tempol** (the first nitroxide shown to have radioprotective properties) and have also identified 3 analogs that radiosensitize aerobic cells. These agents will be evaluated and compared with **tempol** in vivo. We have recently shown that heme proteins exposed to oxidants form highly toxic ferryl moieties and that nitroxides detoxify these toxic species and confer enhanced catalase-like activity to

heme species. Since these agents readily penetrate cell membranes, they may be of use in other areas of medical research such as ischemia/reperfusion injury studies, prevention of cataracts, inflammatory processes and aging.

L4 ANSWER 37 OF 93 MEDLINE DUPLICATE 15
ACCESSION NUMBER: 96200316 MEDLINE
DOCUMENT NUMBER: 96200316
TITLE: Adjunctive treatment of murine neuroblastoma with 6-hydroxydopamine and **Tempol**.
AUTHOR: Purpura P; Westman L; Will P; Eidelman A; Kagan V E; Osipov A N; Schor N F
CORPORATE SOURCE: Department of Pediatrics, University of Pittsburgh, Pennsylvania 15213, USA.
CONTRACT NUMBER: CA47161 (NCI)
SOURCE: CANCER RESEARCH, (1996 May 15) 56 (10) 2336-42.
Journal code: CNF. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199608
AB Currently available therapy for disseminated neuroblastoma affords only a 5-20% 5-year survival rate. We have attempted to design targeted chemotherapy for this disease by exploiting the dopamine uptake system on neuroblastoma cells. 6-Hydroxydopamine (6OHDA) is a neurotransmitter analogue, which generates cytolytic oxygen radicals in neuroblastoma cells that take it up. It is, however, predictably, systemically toxic, because of its spontaneous oxidation. Its toxicity is particularly severe in the sympathetic nervous system, because this tissue selectively concentrates dopamine and its analogues. Lowering the dose of 6OHDA below toxic levels prohibitively compromises its antitumor effect. To avoid both the systemic and sympathetic nervous system toxicity yet retain the antitumor efficacy of 6OHDA, we have used the antioxidant **Tempol** adjunctively with 6OHDA. Administration of **Tempol** (250 mg/kg, i.p.) 10 min prior to administration of toxic doses of 6OHDA (350 or 400 mg/kg, i.p.) resulted in a decrease in the mortality rate, sympathetic nervous system impairment, and activity impairment compared with those seen with 6OHDA alone. **Tumor** weights from mice administered saline or **Tempol** alone were 3.6 +/- 1.9 and 2.9 +/- 0.7 g, respectively. In contrast, mice administered **Tempol** followed by 6OHDA had an average **tumor** weight of 0.7 +/- 0.3 g. **Tumor** incidence was also reduced from 80-100% to 40%. Studies performed using electron spin resonance spectroscopy suggest that **Tempol** acts in this system by reacting directly with both the 6OHDA radical and, in the presence of iron, its oxidation product, the hydroxyl radical.

L4 ANSWER 38 OF 93 MEDLINE DUPLICATE 16
ACCESSION NUMBER: 97149761 MEDLINE
DOCUMENT NUMBER: 97149761
TITLE: Modulatory effect of **tempol** on toxicity and antitumor activity of 6-mercaptopurine and on P450 cytochrome level.
AUTHOR: Konovalova N P; Diatchkovskaya R F; Volkova L M; Varfolomeev V N
CORPORATE SOURCE: Institute of Chemical Physics, Russian Academy of Sciences, Chernogolovka, Moscow Region, Russia.
SOURCE: NEOPLASMA, (1996) 43 (5) 341-6.
Journal code: NVO. ISSN: 0028-2685.
PUB. COUNTRY: Czech Republic

Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199704
ENTRY WEEK: 19970402
AB Low selectivity of contemporary antitumor drugs requires a search for its improvement. In this context, nitroxyl radicals are of interest as promising pharmacological agents. The introduction of nitroxyl radical into the structure of antitumor cytostatics was found to reduce considerably their general and specific toxicity. In this work, we demonstrate a detoxifying effect of **tempol** upon its combined injection with cytostatics at their absolute lethal dose in the intact mice as well as an improvement of sensitivity of **tumor**-bearing animals to 6-MP. **Tempol** is shown to normalize the level of oxidized form of P450 cytochrome in a liver, reduced as a result of the injection of 6-MP.

L4 ANSWER 39 OF 93 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:118514 CAPLUS
DOCUMENT NUMBER: 124:225157
TITLE: Use of nitroxides for assessing perfusion, oxygenation, and viability of tissues: in vivo EPR and MRI studies
AUTHOR(S): Gallez, Bernard; Bacic, Goran; Goda, Fuminori; Jiang, Jinjie; O'Hara, Julia A.; Dunn, Jeff F.; Swartz, Harold M.
CORPORATE SOURCE: Department of Radiology, Dartmouth Medical School, Hanover, NH, 03755, USA
SOURCE: Magn. Reson. Med. (1996), Volume Date 1996, 35(1), 97-106
CODEN: MRMEEN; ISSN: 0740-3194
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Relative perfusion, pO2, and bioredn. were measured simultaneously in vivo in tissues in mice by following changes in the intensity and shape of the EPR spectra of nitroxides injected directly into the tissues, using low frequency (1.1 GHz) localized EPR spectroscopy. Using normal and blood flow restricted gastrocnemius muscles it was shown that the decrease of the EPR signals of the nitroxides in tissues was due principally to perfusion, which redistributed the nitroxides. Changes in pO2 were reflected by changes of the linewidth; only a perdeuterated nitroxide with a narrow line was an adequate indicator for this parameter. This technique was applied exptl. in murine **tumors** (MTG-B and RIF-1) to det. the perfusion and pO2 in these relatively hypoxic model **tumor** systems. Using the paramagnetic properties of the nitroxides to enhance T1-weighted MR images, heterogeneity in perfusion in individual **tumors** was demonstrated.

L4 ANSWER 40 OF 93 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:183463 CAPLUS
DOCUMENT NUMBER: 126:248459
TITLE: Bioreduction of nitroxides in murine **tumors** with blocked thiols in the light of the in vivo ESR data
AUTHOR(S): Elas, Martyna; Cieszka, Krystyna; Matuszak, Zenon; Lukiewicz, Stanislaw
CORPORATE SOURCE: Laboratory for Radiobiology and Radiospectroscopy of Cancer, Institute of Molecular Biology, Jagiellonian University, Krakow, Pol.
SOURCE: Curr. Top. Biophys. (1996), 20(1), 62-66
CODEN: CTOBEU; ISSN: 1232-9630

PUBLISHER: Wydawnictwo Protext
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Treatment with sulfhydryl blockers caused a decrease in the rate of nitroxide free radical (NFR) redn. in melanoma cells under in vitro conditions and in neoplastic tissue in vivo. The tested blockers, Diamide (diazene dicarboxylic acid 1,1-azobis-N,N-dimethylamide) and DEM (di-Et maleate), were equally effective in B16 cells in vitro, whereas in B16 **tumors** growing in situ DEM was more efficient. It was demonstrated that it is possible to alter the redox state of both cells and **tumors** by modifying the level of cellular thiols.

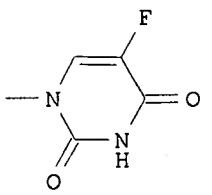
L4 ANSWER 41 OF 93 MEDLINE DUPLICATE 17
ACCESSION NUMBER: 96140768 MEDLINE
DOCUMENT NUMBER: 96140768
TITLE: Modulation of sensitivity to mitomycin C and a dithiol analogue by **tempol** in non-small-cell lung **cancer** cell lines under hypoxia.
AUTHOR: Bando T; Kasahara K; Shibata K; Numata Y; Heki U; Shirasaki H; Iwasa K; Fujimura M; Matsuda T
CORPORATE SOURCE: Third Department of Internal Medicine, Kanazawa University School of Medicine, Japan.
SOURCE: JOURNAL OF CANCER RESEARCH AND CLINICAL ONCOLOGY, (1996) 122 (1) 21-6.
Journal code: HL5. ISSN: 0171-5216.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199604
AB We examined the mechanisms involved in the bioactivation of mitomycin C (MMC) and a newly developed MMC analogue: 7-N-(2-([2-(gamma-L-glutamylamino)ethyl]dithio)ethyl)mitomycin C, KW-2149, in non-small-cell lung **cancer** (NSCLC) cell lines under aerobic and hypoxic conditions. To investigate these mechanisms, we used MMC-resistant non-small-cell lung **cancer** cell lines (PC-9/MC4) that had been established in our laboratory from the parent PC-9 cell line by continuous exposure to MMC. We previously reported that the MMC-resistant cell line (PC-9/MC4) was poor in NAD(P)H dehydrogenase (quinone) activity and approximately 6-fold more resistant than the parent cells (PC-9) to MMC on 2-h exposure under aerobic conditions. In this study, the subline PC-9/MC4 was 6.7-fold more resistant to MMC than PC-9, the parent cell line, under aerobic conditions, and 5.2-fold more resistant under hypoxic conditions after 2-h exposure to MMC. However, on co-incubation with **tempol**, an inhibitor of the one-electron reduction pathway, the sensitivity of PC-9/MC4 to MMC was impaired under hypoxic conditions, but the impairment was not evident under aerobic conditions. KW-2149, the newly developed MMC analogue, was cytotoxic for both PC-9/MC4 and PC-9 cells, and the sensitivity of both cell lines to KW-2149 was not changed by exposure to hypoxic conditions or by coincubation with **tempol**. There were no significant differences in the intracellular uptake of MMC and the activities of cytosolic detoxification enzymes between the PC-9 and PC-9/MC4 cell lines. These results support the hypothesis that the one-electron reduction pathway plays a partial role in the bioactivation of MMC, but not of KW-2149, and that KW-2149 is excellent at circumventing resistance to MMC in NSCLC.

L4 ANSWER 42 OF 93 TOXLINE

ACCESSION NUMBER: 1996:2505 TOXLINE
DOCUMENT NUMBER: CRISP-96-CM06387-08
TITLE: NITROXIDES AS PROTECTORS AGAINST OXIDATIVE STRESS.
AUTHOR: RUSSO A
CORPORATE SOURCE: NCI, NIH
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, DIVISION OF CANCER TREATMENT.
CONTRACT NUMBER: 1Z01CM06387-08
SOURCE: (1995). Crisp Data Base National Institutes Of Health. Award Type: A = Intramural Project
DOCUMENT TYPE: (RESEARCH)
FILE SEGMENT: CRISP
LANGUAGE: English
ENTRY MONTH: 199604

AB RPROJ/CRISP Nitroxides which have been used as EPR spin labels have been shown to exhibit superoxide dismutase (SOD) activity and are quite effective agents in protecting cells against a wide variety of oxidative stresses including hydrogen peroxide, superoxide, organic hydroperoxides, redox-cycling chemotherapy drugs, and ionizing radiation. We have demonstrated that **Tempol** protects both cells in vitro and mice against ionizing radiation. Thus, the nitroxides represent a new class of radiation protectors that may have widespread use in protecting humans against radiation. Preliminary studies using a rodent **tumor** model have shown that **tempol** does not protect **tumor** tissue. The mechanism of this finding may involve differential metabolic reduction properties of normal versus **tumor**. Additionally, work has begun to identify the most efficient nitroxide for protection purposes. We have recently evaluated approximately 110 nitroxides in a structure activity relationship study. These nitroxides were kindly given to us from Dr. Hideg of Hungary, an international expert on nitroxide synthesis. We have identified 6 nitroxides that afford significantly more radioprotection than **tempol** (the first nitroxide shown to have radioprotective properties). Interestingly, we have also identified 3 analogs that radiosensitize aerobic cells. Mechanistic studies are underway to explore this finding. We have also demonstrated that nitroxides administered to animals after local irradiation to the kidney offers significant protection. More recently we have been investigating the mechanism by which these agents stimulate catalase like activity in heme proteins which otherwise would in combination produce highly toxic oxidants. Since these agents readily penetrate cell membranes, they may be of use in other areas of medical research such as ischemia/reperfusion injury studies. Furthermore, these studies have opened the possibility of interrelating the biochemistry and metabolism of nitroxides to endogenously produced endothelial relaxation factor, nitric oxide.

L4 ANSWER 43 OF 93 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:785636 CAPLUS
DOCUMENT NUMBER: 123:313863
TITLE: Syntheses and antitumor activities of new spin-labeled 5-fluorouracil derivatives(III)
AUTHOR(S): Wang, Yan-Guang; Chen, Yao-Zu; Xiao, Xin-Liang; Liu, Rui-Xian
CORPORATE SOURCE: Dep. of Chemistry, Zhejiang Univ., Hangzhou, 310027, Peop. Rep. China
SOURCE: Gaodeng Xuexiao Huaxue Xuebao (1995), 16(6), 896-9
CODEN: KTHPDM; ISSN: 0251-0790
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
GI



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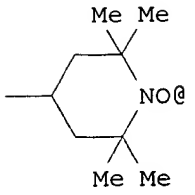

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AB Title compds. QCONHQ1 (I), QCONHCHRCONHQ1 (II; R = H, Me2CHCH2, PhCH2, Me, Me2CH), and QNHCHR1CO2Q1 (R1 = H, Me2CHCH2, PhCH2) were synthesized and their structures were confirmed by IR, UV, MS and ESR spectra as well as elementary anal. The antitumor activities of I and II were tested against S180 and EAC in mice. The preliminary results showed that the antitumor activities of II (R = Me2CH) was similar to that of 5-fluorouracil, while the acute toxicity of II (R = Me2CH) (LD50 = 944.8 mg/kg) was about 8 times lower than that of 5-fluorouracil (LD50 = 117.2 mg/kg).

L4 ANSWER 44 OF 93 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 18
ACCESSION NUMBER: 1995:911084 CAPLUS
DOCUMENT NUMBER: 124:372
TITLE: Cytotoxicity of a novel indoloquinone EO9 in hypoxic non-small-cell lung **cancer** cell lines
AUTHOR(S): Bando, Takuma; Kasahara, Kazuo; Shibata, Kazuhiko; Numata, Yuka; Heki, Utako; Shirasaki, Hiroki; Iwasa, Kei-Ichi; Fujimura, Masaki; Matsuda, Tamotsu
CORPORATE SOURCE: School Medicine, Kanazawa University, Kanazawa, Japan
SOURCE: Int. J. Oncol. (1995), 7(4), 789-93
CODEN: IJONES; ISSN: 1019-6439
DOCUMENT TYPE: Journal
LANGUAGE: English

AB EO9 is a bioreductive anticancer agent active on non-small-cell lung **cancer** (NSCLC) and structurally related to mitomycin C (MMC). DT-diaphorase (DTD) is regarded as a 2-electron reductase that plays an important role in the biotransformation of MMC to antitumor metabolites. To evaluate the role of DTD as a bioactivator of EO9 in NSCLC cell lines under normoxic and hypoxic conditions, expts. were done to examine the inhibitory effect of dicumarol, a selective inhibitor of DTD, on the sensitivity to EO9 in vitro. This study used an MMC-resistant NSCLC cell line (PC-9/MC4) which was established from a parent PC-9 cell line by continuous exposure to MMC. The subline PC-9/MC4 was 6.7-fold more resistant to MMC than was PC-9, and had decreased DTD activity. The IC50 value of EO9 against PC-9 was increased by co-incubation with dicumarol under normoxic conditions. EO9 was more cytotoxic against PC-9/MC4 than against PC-9 cells and the enhancement was impaired by **tempol** under hypoxic conditions. These findings suggest a suppressive role of DTD against a 1-electron redn. pathway in the bioactivation of EO9 under hypoxic conditions; EO9 may be active against O-deficient solid **tumors**, esp. in MMC-resistant NSCLC cells with low levels of DTD activity.

L4 ANSWER 45 OF 93 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 19
ACCESSION NUMBER: 1995:255845 BIOSIS
DOCUMENT NUMBER: PREV199598270145
TITLE: Molecular mechanisms of tirapazamine (SR 4233, WIN 59072)-induced hepatocyte toxicity under low oxygen concentrations.
AUTHOR(S): Khan, S. (1); O'Brien, P. J.
CORPORATE SOURCE: (1) Fac. Pharmacy, Univ. Toronto, 19 Russell Street, Toronto, ON M5S 2S2 Canada

SOURCE: British Journal of Cancer, (1995) Vol. 71, No. 4, pp. 780-785.
ISSN: 0007-0920.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Previously we showed that tirapazamine (SR 4233, Win 59075) is cytotoxic towards hepatocytes under conditions of hypoxia but not in 10% or 95% oxygen and that bioreduction by DT-diaphorase or cytochrome P450 is not a major pathway. In the present study, we report that tirapazamine is highly cytotoxic to isolated rat hepatocytes maintained under 1% oxygen and the molecular cytotoxic mechanism has been elucidated. Cytotoxicity was prevented by the cytochrome P450 2E1 inhibitors phenyl imidazole, isoniazid, isopropanol or ethanol, suggesting that cytochrome P450 2E1 catalyzed tirapazamine reductive bioactivation. By contrast, dicumarol, a DT-diaphorase inhibitor, markedly increased tirapazamine-induced cytotoxicity. Cytotoxicity was also inhibited in normal but not DT-diaphorase-inactivated hepatocytes by increasing cellular NADH levels with lactate or ethanol or the mitochondrial respiratory inhibitors. Evidence that oxygen activation contributed to cytotoxicity was that glutathione oxidation occurred well before cytotoxicity ensued and that tirapazamine was more cytotoxic towards catalase- or glutathione reductase-inactivated hepatocytes. Furthermore, polyphenolic antioxidants such as quercetin, caffeic acid or purpurogallin, the radical trap **Tempol** or the iron chelator desferrioxamine prevented tirapazamine-mediated cytotoxicity. However, the antioxidants diphenylphenylenediamine, butylated hydroxyanisole or butylated hydroxytoluene did not prevent cytotoxicity and malonaldehyde formation was not increased, suggesting that lipid peroxidation was not important. The above results suggest that DT-diaphorase detoxifies tirapazamine whereas reduced cytochrome P450 reduces tirapazamine to a nitrogen oxide anion radical which forms cytotoxic reactive oxygen species as a result of redox cycling.

L4 ANSWER 46 OF 93 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95168167 EMBASE
DOCUMENT NUMBER: 1995168167
TITLE: Nitric oxide and anti-**cancer** therapy.
AUTHOR: Sagar S.M.; Singh G.; Hodson D.I.; Whitton A.C.
CORPORATE SOURCE: Hamilton Regional Cancer Centre, 699 Concession Street,Hamilton, Ont. L8V 5C2, Canada
SOURCE: Cancer Treatment Reviews, (1995) 21/2 (159-181).
ISSN: 0305-7372 CODEN: CTREDJ
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English

L4 ANSWER 47 OF 93 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1996:110379 BIOSIS
DOCUMENT NUMBER: PREV199698682514
TITLE: Nitroxide radicals, modificators of toxic action of cytostatics.
AUTHOR(S): Konovalova, N. P.
CORPORATE SOURCE: Inst. Chem. Phys., Russ. Acad. Sci., Chernogolovka Russia
SOURCE: Voprosy Onkologii (St. Petersburg), (1995) Vol. 41, No. 2, pp. 49-50.
ISSN: 0507-3758.
DOCUMENT TYPE: Article
LANGUAGE: Russian

L4 ANSWER 48 OF 93 TOXLINE
ACCESSION NUMBER: 1995:206868 TOXLINE
DOCUMENT NUMBER: CRISP-95-CM06387-07
TITLE: NITROXIDES AS PROTECTORS AGAINST OXIDATIVE STRESS.
AUTHOR: RUSSO A
CORPORATE SOURCE: NCI, NIH
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, DIVISION OF CANCER TREATMENT.
CONTRACT NUMBER: 1Z01CM06387-07
SOURCE: (1994). Crisp Data Base National Institutes Of Health.
Award Type: A = Intramural Project
DOCUMENT TYPE: (RESEARCH)
FILE SEGMENT: CRISP
LANGUAGE: English
ENTRY MONTH: 199507
AB RPROJ/CRISP Nitroxides which have been used as EPR spin labels have been shown to exhibit superoxide dismutase (SOD) activity and are quite effective agents in protecting cells against a wide variety of oxidative stresses including hydrogen peroxide, superoxide, organic hydroperoxides, redox-cycling chemotherapy drugs, and ionizing radiation. We have demonstrated that **Tempol** protects both cells in vitro and mice against ionizing radiation. Thus, the nitroxides represent a new class of radiation protectors that may have widespread use in protecting humans against radiation. Preliminary studies using a rodent **tumor** model have shown that **Tempol** does not protect **tumor** tissue. The mechanism of this finding may involve differential metabolic reduction properties of normal versus **tumor**. Additionally, work has begun to identify the most efficient nitroxide for protection purposes. We are currently evaluating approximately 75 nitroxides in a structure-activity relationship study. These nitroxides were kindly given to us from Dr. Hideg of Hungary, an international expert on nitroxide synthesis. We are presently screening the compounds in vitro and when appropriate candidates are identified in vivo testing will begin. Preliminary studies have identified at least 3 agents which provide more in vitro radioprotection than **Tempol** (the nitroxide used for all the studies noted above). Unexpectedly, we have also identified a novel non- toxic radiation sensitizer in this screen and further work is being conducted to determine the mechanism for this interesting finding. Since these agents readily penetrate cell membranes, they may be of use in other areas of medical research such as ischemia/reperfusion injury studies. Furthermore, these studies have opened the possibility of inter-relating the biochemistry and metabolism of nitroxides to endogenously produced endothelial relaxation factor, nitric oxide.

DUPLICATE 20

L4 ANSWER 49 OF 93 MEDLINE
ACCESSION NUMBER: 94185063 MEDLINE
DOCUMENT NUMBER: 94185063
TITLE: Potential use of nitroxides in radiation oncology.
AUTHOR: Hahn S M; Krishna C M; Samuni A; DeGraff W; Cuscela D O; Johnstone P; Mitchell J B
CORPORATE SOURCE: Radiation Biology Section, National Cancer Institute, NIH, Bethesda, Maryland 20892.
SOURCE: CANCER RESEARCH, (1994 Apr 1) 54 (7 Suppl) 2006s-2010s.
Ref: 43
Journal code: CNF. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals

ENTRY MONTH: 199406

AB The identification of radioprotectors is an important goal for those involved in radiation oncology and for those interested in the investigation of the mechanisms of radiation cytotoxicity. Recently, a new class of in vitro and in vivo radioprotectors, the nitroxides, has been discovered. The nitroxides are low-molecular-weight stable free radicals which are freely membrane permeable and which have been shown to act as superoxide dismutase mimics. Further investigation of these compounds has shown that a water-soluble nitroxide, **Tempol**, protects cultured Chinese hamster V79 cells from the cytotoxicity caused by superoxide, hydrogen peroxide, and t-butyl hydroperoxide. **Tempol** and five other water-soluble nitroxides have also been shown to protect V79 cells against radiation-induced cytotoxicity. Potential mechanisms of protection by the nitroxides include oxidation of reduced transition metals, superoxide dismutase-like activity, and scavenging of oxy- and carbon-based free radicals. In vivo studies reveal that **Tempol** protects C3H mice from the lethal effects of radiation with a dose causing 50% lethality within 30 days of 9.97 Gy and 7.84 Gy in **Tempol**-treated and saline-treated mice, respectively, and a dose modification factor of 1.3. The nitroxides represent a new class of non-thiol radioprotectors which may also have application as general antioxidants. Additional work is necessary to screen other nitroxides for in vivo radioprotection and toxicity as well as to fully evaluate the extent to which these compounds protect **tumors**.

L4 ANSWER 50 OF 93 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1994:264641 CAPLUS
DOCUMENT NUMBER: 120:264641
TITLE: Potential use of nitroxides in radiation oncology
AUTHOR(S): Hahn, Stephen M.; Krishna, C. Murali; Samuni, Amram; DeGraff, William; Cuscela, Daniel O.; Johnstone, Peter; Mitchell, James B.
CORPORATE SOURCE: Radiat. Biol. Sect., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SOURCE: Cancer Res. (1994), 54(7, Suppl.), 2006s-2010s
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 43 refs. The identification of radioprotectors is an important goal for those involved in radiation oncol. and for those interested in the investigation of the mechanisms of radiation cytotoxicity. Recently, a new class of in vitro and in vivo radioprotectors, the nitroxides, has been discovered. The nitroxides are low-mol.-wt. stable free radicals which are freely membrane permeable and which have been shown to act as superoxide dismutase mimics. Further investigation of these compds. has shown that a water-sol. nitroxide, **Tempol**, protects cultured Chinese hamster V79 cells from the cytotoxicity caused by superoxide, hydrogen peroxide, and tert-Bu hydroperoxide. **Tempol** and five other water-sol. nitroxides have also been shown to protect V79 cells against radiation-induced cytotoxicity. Potential mechanisms of protection by the nitroxides include oxidn. of reduced transition metals, superoxide dismutase-like activity, and scavenging of oxy- and carbon-based free radicals. In vivo studies reveal that **Tempol** protects C3H mice from the lethal effects of radiation with a dose causing 50% lethality within 30 days of 9.97 Gy and 7.84 Gy in **Tempol**-treated and saline-treated mice, resp., and a dose modification factor of 1.3. The nitroxides represent a new class of non-thiol radioprotectors which may also have application as general antioxidants. Addnl. work is necessary to screen other nitroxides for in vivo radioprotection and toxicity as well as to fully evaluate the

extent to which these compds. protect **tumors**.

L4 ANSWER 51 OF 93 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:426234 CAPLUS
DOCUMENT NUMBER: 121:26234
TITLE: In the Search for New Anticancer Drugs. 26. A Comparison of Anticancer Activities of Several TEPA, Thio-TEPA, Seleno-TEPA, Aziridine, and Azetidine Analogs, Including Congeners Containing an Aminoxyl Moiety
AUTHOR(S): Sosnovsky, George; Lukszo, Jan; Konieczny, Maria; Purgstaller, Klaus; Laib, Frank
CORPORATE SOURCE: Department of Chemistry, University of Wisconsin, Milwaukee, WI, 53201, USA
SOURCE: J. Pharm. Sci. (1994), 83(7), 982-8
CODEN: JPMSAE; ISSN: 0022-3549
DOCUMENT TYPE: Journal
LANGUAGE: English
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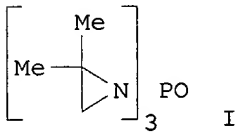


I

AB A series of thio, seleno, aziridine, and azetidine analogs of phosphine oxide, including congeners contg. an aminoxyl moiety, were synthesized and evaluated in vivo for anticancer activity against the murine lymphocytic leukemia P388. All aziridine derivs. were found to be active with an increase in life span ranging from 42% to 272%, and all azetidine analogs were rate as inactive with on marginal exception. An attempt was made to rationalize the results on the basis of the lipophilic properties of the compds. The most active compd. (I) possessed the most balanced lipophilic properties, corresponding to a log P value near zero.

L4 ANSWER 52 OF 93 MEDLINE DUPLICATE 21
ACCESSION NUMBER: 94335598 MEDLINE
DOCUMENT NUMBER: 94335598
TITLE: Measurement of the intracellular concentration of oxygen in a cell perfusion system.
AUTHOR: Chen K; Ng C E; Zweier J L; Kuppusamy P; Glickson J D; Swartz H M
CORPORATE SOURCE: Department of Radiology and Radiological Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland.
CONTRACT NUMBER: GM 34250 (NIGMS)
CA 51935 (NCI)
51950
+
SOURCE: MAGNETIC RESONANCE IN MEDICINE, (1994 Jun) 31 (6) 668-72.
Journal code: MHR. ISSN: 0740-3194.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199411
AB [O2] was measured in the embedding material (alginate) in a typical

apparatus for conducting studies of viable cells with NMR, using low frequency EPR. In suspension cultures respiration was independent of [O2] in the perfusing media down to about 1 microM while in alginate beads, the comparable value was 70 microM, indicating that the alginate was a very substantial barrier to the free diffusion of oxygen. With knowledge of [O2] in the various compartments, [O2] in the perfusing medium can be increased and the full power of NMR can be used to provide information on metabolism under various conditions. These results also provide evidence supporting the feasibility and usefulness of EPR techniques using nitroxides to measure [O2] in macroscopic samples such as NMR perfusion tubes. This technique is rapid, apparently nonperturbing, and enables one to differentiate between the concentrations of oxygen in different compartments.

L4 ANSWER 53 OF 93 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1994:291544 BIOSIS
DOCUMENT NUMBER: PREV199497304544
TITLE: Protection against hypoxia-mediated SR-4233 cytotoxicity by the stable nitroxide free radical **Tempol**.
AUTHOR(S): Herscher, L. L. (1); Krishna, C. M.; Degraff, W.; Mitchell, J. B.; Russo, A.
CORPORATE SOURCE: (1) Radiat. Oncol. Branch, Natl. Cancer Inst., Bethesda, MD 20892 USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (1994) Vol. 35, No. 0, pp. 634. Meeting Info.: 85th Annual Meeting of the American Association for Cancer Research San Francisco, California, USA April 10-13, 1994
ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 54 OF 93 MEDLINE DUPLICATE 22
ACCESSION NUMBER: 94252906 MEDLINE
DOCUMENT NUMBER: 94252906
TITLE: Modification of the aerobic cytotoxicity of etanidazole.
AUTHOR: Palayoor S T; Bump E A; Malaker K; Langley R E; Saroff D M; Delfs J R; Hurwitz S J; Coleman C N
CORPORATE SOURCE: Joint Center for Radiation Therapy, Harvard Medical School, Boston, MA 02115.
CONTRACT NUMBER: CA 42391 (NCI)
SOURCE: INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY, BIOLOGY, PHYSICS, (1994 May 15) 29 (2) 289-93.
Journal code: G97. ISSN: 0360-3016.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199409
AB PURPOSE: To determine the feasibility of modifying the aerobic cytotoxicity of etanidazole without interfering with the tumoricidal action of radiation plus etanidazole. METHODS AND MATERIALS: The aerobic cytotoxicity of etanidazole was studied using two different models: (1) Induction of apoptosis in EL4 cells: apoptotic DNA fragmentation was analyzed by agarose gel electrophoresis following 24 h treatment with etanidazole alone or in combination with various modifiers. (2) Spinal cord neuronal loss in organotypic roller tube cultures: Survival of acetylcholinesterase positive ventral horn neurons was analyzed

morphometrically following 72 h treatment with etanidazole alone or in combination with vitamin E succinate. RESULTS: Etanidazole (10 mM) induced apoptosis in EL4 cells. This effect was suppressed by 24 h treatment with TPA, IBMX, the free radical scavenger **TEMPOL** or vitamin E succinate. Vitamin E succinate also protected spinal cord cultures from etanidazole-induced neuronal loss. CONCLUSION: These results suggest that it might be possible to modify the neurotoxicity of etanidazole with agents that would not be expected to interfere with the tumoricidal action of radiation plus etanidazole.

L4 ANSWER 55 OF 93 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1995:237392 BIOSIS
DOCUMENT NUMBER: PREV199598251692
TITLE: Adjunctive treatment of murine neuroblastoma with 6-hydroxydopamine (OHDA) and **tempol**.
AUTHOR(S): Purpura, Patti (1); Westman, Laurel; Will, Patricia; Eidelman, Anthony; Schor, Nina Felice
CORPORATE SOURCE: (1) Dep. Ped., Univ. Pittsburgh, Pittsburgh, PA USA
SOURCE: Pediatric Research, (1994) Vol. 37, No. 4 PART 2, pp. 164A.
Meeting Info.: 105th Annual Meeting of the American Pediatric Society and the 64th Annual Meeting of the Society for Pediatric Research San Diego, California, USA May 7-11, 1995
ISSN: 0031-3998.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 56 OF 93 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1994:474548 BIOSIS
DOCUMENT NUMBER: PREV199497487548
TITLE: Novel radiation protectors.
AUTHOR(S): Mitchell, James B. (1); Hahn, Stephen (1); Liebmann, James (1); Cook, John (1); Krishna, Murali (1); Russo, Angelo (1); Wink, David
CORPORATE SOURCE: (1) Radiation Biol. Branch, Natl. Cancer Inst., Bethesda, MD 20892 USA
SOURCE: International Journal of Radiation Oncology Biology Physics, (1994) Vol. 30, No. SUPPL. 1, pp. 101.
Meeting Info.: 36th Annual Meeting of the American Society for Therapeutic Radiology and Oncology San Francisco, California, USA October 2-6, 1994
ISSN: 0360-3016.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 57 OF 93 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1994:259333 BIOSIS
DOCUMENT NUMBER: PREV199497272333
TITLE: Polymerase chain reaction-directed DNA sequencing of bleomycin-induced "nondeletion"-type, 6-thioguanine-resistance mutants in Chinese hamster ovary cell derivative AS52: Effects of an inhibitor and a mimic of superoxide dismutase.
AUTHOR(S): An, Jie (1); Hsie, Abraham W.
CORPORATE SOURCE: (1) Dep. Preventive Med. and Community Health, Univ. Tex. Med. Branch, 2.102 Ewing Hall, J-10, Galveston, TX 77555-1010 USA
SOURCE: Environmental and Molecular Mutagenesis, (1994) Vol. 23, No. 2, pp. 101-109.
ISSN: 0893-6692.
DOCUMENT TYPE: Article

LANGUAGE: English

AB Bleomycin-induced, 6-thioguanine-resistant, 'non deletion' mutants pretreated with or without either TRIEN (triethylenetetramine), a superoxide dismutase (SOD) inhibitor, or **TEMPOL** (4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl), a SOD mimic, were analyzed by polymerase chain reaction (PCR)-directed DNA sequencing in a Chinese hamster ovary (CHO) cell derivative, AS52. Among the 23 bleomycin-induced mutants, six have 3-bp 5'-TGA-3' deletions in the region of 366-371, five have single-base deletions, seven have base substitutions, three have insertions, and two have possible translocations. Among the 16 bleomycin-induced mutants pretreated with TRIEN, six have the 5'-TGA-3' deletion (366-371), two have single-base deletions, one has a 13-bp deletion, four have single-base substitutions, one has a double-base substitution, and two have insertions. Among the 17 bleomycin-induced mutants pretreated with **TEMPOL**, six have the same TGA deletions, two have single-base deletions, two have single-base insertions, four have single-base substitutions, one mutant has a 12-bp deletion, one has a 13-bp deletion, and one mutant shows no detectable change in its coding region in the DNA sequence. A possible shift from a ROS-mediated mutational spectrum to a spontaneous mutational spectrum by TRIEN further indicates that reactive oxygen species play an important role in bleomycin mutagenesis in mammalian cells.

L4 ANSWER 58 OF 93 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 94364682 EMBASE

DOCUMENT NUMBER: 1994364682

TITLE: Apoptosis and a re-investigation of the biologic basis for **cancer** therapy.

AUTHOR: D'Amico A.V.; McKenna W.G.

CORPORATE SOURCE: Department of Radiation Oncology, Hosp. of University of Pennsylvania, 2-Domer Building, 3400 Spruce Street,Philadelphia, PA 19104, United States

SOURCE: Radiotherapy and Oncology, (1994) 33/1 (3-10). ISSN: 0167-8140 CODEN: RAONDT

COUNTRY: Ireland

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 006 Internal Medicine
014 Radiology
016 Cancer
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Antitumor therapy has expanded beyond the previous notions of cytotoxic or biologic therapy to now include agents that induce differentiation (e.g. all trans-retinoic acid for induction of complete remission in patients with acute promyelocytic leukemia [23]) or apoptosis [91]. In fact, the phenomenon of apoptosis may be fundamental to the current understanding of carcinogenesis [11] and may also underlie the effectiveness of some forms of chemotherapy [4,5,18,39,56,59,67], radiation therapy [19,44,52,60,64, 77,78,85] and the interferons [73]. The process of apoptosis has been shown to be responsible for the normal elimination of cells with damaged DNA [81] as well as other potentially dangerous cells such as autoreactive T-lymphocytes [14]. Therefore, although much attention has been given to oncogenes that induce cellular proliferation, one can easily see how the same result (i.e. neoplasia) could be obtained when the ability of a cell to undergo apoptosis is lost.

L4 ANSWER 59 OF 93 TOXLINE

ACCESSION NUMBER: 1994:55576 TOXLINE

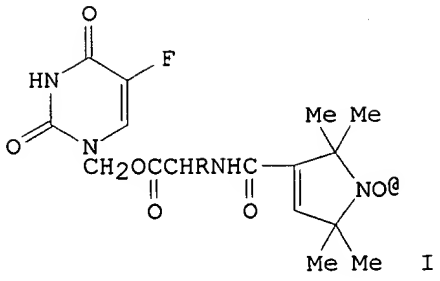
DOCUMENT NUMBER: CRISP-94-CM06387-06

TITLE: DEVELOPMENT OF SUPEROXIDE DISMUTASE MIMICS.

AUTHOR: RUSSO A
CORPORATE SOURCE: NCI, NIH
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, DIVISION OF CANCER TREATMENT.
CONTRACT NUMBER: 1Z01CM06387-06
SOURCE: (1993). Crisp Data Base National Institutes Of Health. Award Type: A = Intramural Project
DOCUMENT TYPE: (RESEARCH)
FILE SEGMENT: CRISP
LANGUAGE: English
ENTRY MONTH: 199403

AB RPROJ/CRISP Our laboratory has shown that nitroxides, which have been used as EPR spin labels exhibit superoxide dismutase (SOD) activity and are quite effective agents in protecting cells against a wide variety of oxidative stresses. Our lead compound, **Tempol**, a water soluble nitroxide has been shown to protect mammalian cells against superoxide generated from xanthine/xanthine oxidase, and direct hydrogen peroxide cytotoxicity. We have demonstrated that **Tempol** protects both cells in vitro and mice against ionizing radiation. Thus, the nitroxides represent a new class of radiation protectors that may have widespread use in protecting humans against radiation. Preliminary studies using a rodent **tumor** model have shown that **Tempol** does not protect **tumor** tissue. Further chemical characterization of the SOD mimic activity of nitroxides has revealed the presence of an oxoammonium cation intermediate. This information will be used to identify for maximal protective capacity based on their oxidation potential and charge. **Tempol** has been shown to protect cells against mutation induction mediated by superoxide, hydrogen peroxide, and radiation. **Tempol** has also been shown to protect cells exposed to various chemotherapy drugs including mitomycin C and SR-4233. Not only might these agents be useful in protecting against certain chemotherapy agents but should be instructive in determining mechanisms of action. Topically applied, **Tempol** has been shown to protect against radiation- induced alopecia in guinea pigs. It has also been shown to be a novel class of anti-ulcerogenic compounds. Since these agents readily penetrate cell membranes, they may be of use in other areas of medical research such as ischemia/reperfusion injury studies. Furthermore, these studies have opened the possibility of inter-relating the biochemistry and metabolism of nitroxides to endogenously produced endothelial relaxation factor, nitric oxide.

L4 ANSWER 60 OF 93 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:435515 CAPLUS
DOCUMENT NUMBER: 121:35515
TITLE: Syntheses and antitumor activities of new spin-labeled 5-fluorouracil derivatives
AUTHOR(S): Wang, Yanguang; Tian, Xuan; Li, Jingxin; Chen, Yaozu
CORPORATE SOURCE: Chem. Dep., Tianjin Univ., Tianjin, 300072, Peop. Rep. China
SOURCE: Gaodeng Xuexiao Huaxue Xuebao (1993), 14(10), 1399-401
CODEN: KTHPDM; ISSN: 0251-0790
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
GI



I

AB A series of new spin-labeled 5-fluorouracil derivs., as potential antitumor agents, were synthesized, and their structures were confirmed by IR, UV, MS and ESR spectra as well as elemental anal. Preliminary results showed that compds. I (R = H, Me, Ph) showed antitumor activity comparable to that of 5-fluorouracil.

L4 ANSWER 61 OF 93 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93223810 EMBASE
DOCUMENT NUMBER: 1993223810
TITLE: Recent advances in radioprotective agents.
AUTHOR: Edwards M.L.; Snyder R.D.
CORPORATE SOURCE: Marion Merrell Dow Research Inst, 2110 East Galbraith Road,Cincinnati, OH 45215, United States
SOURCE: Current Opinion in Therapeutic Patents, (1993) 3/6 (767-779).
ISSN: 0962-2594 CODEN: COTPES
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine
014 Radiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English

L4 ANSWER 62 OF 93 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:400462 BIOSIS
DOCUMENT NUMBER: PREV199345059287
TITLE: The radioprotector **tempol** does not decrease radiation-induced RIF **tumor** control in C3H mice.
AUTHOR(S): Hahn, S. M.; Sullivan, F.; Deluca, A. M.; Krishna, M. C.; Glass, J.; Russo, A.; Mitchell, J. B.
CORPORATE SOURCE: Radiation Oncology Branch, NCI, NIH, Bethesda, MD USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (1993) Vol. 34, No. 0, pp. 433.
Meeting Info.: 84th Annual Meeting of the American Association for Cancer Research Orlando, Florida, USA May 19-22, 1993
ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 63 OF 93 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:400461 BIOSIS
DOCUMENT NUMBER: PREV199345059286
TITLE: Stem cell factor (SCF) and **tempol** act in synergy to protect mice from lethal irradiation.
AUTHOR(S): Liebmann, J. (1); Deluca, A. M. (1); Epstein, A. (1); Steinberg, S.; Russo, A. (1); Mitchell, J. B. (1)

CORPORATE SOURCE: (1) Radiation Oncology Branch, NCI, NIH, Bethesda, MD USA
SOURCE: Proceedings of the American Association for Cancer Research
Annual Meeting, (1993) Vol. 34, No. 0, pp. 433.
Meeting Info.: 84th Annual Meeting of the American Association for Cancer Research Orlando, Florida, USA May 19-22, 1993
ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 64 OF 93 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1994:113238 BIOSIS
DOCUMENT NUMBER: PREV199497126238
TITLE: Modifiers of radiation-induced apoptosis.
AUTHOR(S): Langley, Ruth E.; Palayoor, Sanjeewani T.; Coleman, C. Norman; Bump, Edward A.
CORPORATE SOURCE: Joint Cent. Radiation Therapy, Harvard Med. Sch., Dana Farber Cancer Inst., Boston, MA 02115 USA
SOURCE: Radiation Research, (1993) Vol. 136, No. 3, pp. 320-326.
ISSN: 0033-7587.
DOCUMENT TYPE: Article
LANGUAGE: English
AB EL4 murine lymphoma cells and F9 murine teratocarcinoma cells undergo apoptosis-like cell death after exposure to ionizing radiation. Apoptosis differs in several ways from classical clonogenic cell killing by radiation. We have tested several modifiers and radiomimetic agents in an effort to determine if the mechanism of induction of apoptosis by radiation differs from the mechanism of classical clonogenic cell killing by radiation, and consequently that these two end points of radiation action might be differentially modifiable. We found that internucleosomal DNA fragmentation, characteristic of apoptosis, can result from treatment of EL4 and F9 cells with agents that have diverse modes of action: tert-butyl hydroperoxide, diazenedicarboxylic acid bis(N,N-piperidide), and etoposide. Hydrogen peroxide did not induce internucleosomal DNA fragmentation at concentrations expected to be produced by the doses of ionizing radiation that we used. Radiation-induced DNA fragmentation could be inhibited by 3-aminobenzamide, dibutryl cyclic AMP, or 4-hydroxy-2,2,6,6,-tetramethylpiperidine-N-oxyl, although in this respect there appear to be marked differences between the cell lines.

L4 ANSWER 65 OF 93 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:517802 BIOSIS
DOCUMENT NUMBER: PREV199345116427
TITLE: Protection from radiation-induced alopecia with topical application of nitroxides: Fractionated studies.
AUTHOR(S): Cuscela, Daniel; Coffin, Deborah; Muldoon, Rebecca; Glass, Joe; Krishna, Murali C.; Bernstein, Eric; Mitchell, James B.
CORPORATE SOURCE: Radiation Biol. Sect., Radiation Oncology Branch, Natl. Cancer Inst., Natl. Inst. Health, Bethesda, MD USA
SOURCE: International Journal of Radiation Oncology Biology Physics, (1993) Vol. 27, No. SUPPL. 1, pp. 197.
Meeting Info.: 35th Annual Meeting of the American Society for Therapeutic Radiology and Oncology New Orleans, Louisiana, USA October 11-15, 1993
ISSN: 0360-3016.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 66 OF 93 CANCERLIT
ACCESSION NUMBER: 94699777 CANCERLIT
DOCUMENT NUMBER: 94699777
TITLE: Potential use of nitroxides in radiation oncology (Meeting

abstract).
AUTHOR: Mitchell J B; Krishna M C; Hahn S; Liebmann J; Cook J A; DeGraff W; Cuscela D; Sullivan F; Johnstone P; Gamson J; et al
CORPORATE SOURCE: Radiation Biology Section, Radiation Oncology Branch, NCI, Bethesda, MD.
SOURCE: Non-serial, (1993). Anticarcinogenesis and Radiation Protection, 4th International Conference:Mechanisms, Biomarkers, Molecular Diagnostics and Preventive Strategies. April 18-23, 1993, Baltimore, Maryland.
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
FILE SEGMENT: ICDB
LANGUAGE: English
ENTRY MONTH: 199411

AB There is a continued need to improve the effectiveness of radiation treatment of human malignancies. We have recently identified a new class of non-thiol radioprotectors that may have utility in clinical radiotherapy. Nitroxides which have already found considerable utility both in ESR and NMR spectroscopy, were recently shown to exhibit superoxide dismutase mimetic activity and were capable of protecting mammalian cells against superoxide and hydrogen peroxide cytotoxicity. Since ionizing radiation in an oxygen environment produces superoxide, hydrogen peroxide, and hydroxyl radical, we anticipated that nitroxides might also provide protection against radiation. In vitro aerobic radiation survival studies using Chinese hamster cells pretreated with both 5- and 6-membered ring nitroxides revealed radiation protection factors which ranged from 1.2 to 2.4 at a concentration of 10 mM. Protection was observed only for the oxidized form of nitroxide-reduced forms (hydroxylamines) were not protective. Interestingly, one nitroxide (**tempol**) was shown to sensitize hypoxic cells to radiation. In mice, the maximally tolerated dose of **tempol** (275 mg/kg) given 10 min before whole body irradiation gave a 1.3 protection factor at the LD 50/30. Preliminary studies have also been initiated to determine if **tempol** protects **tumor** in addition to normal tissues. TCD50 studies of the murine RIF **tumor** in the presence or absence of **tempol** has shown no protection. Thus, our preliminary studies establish nitroxides as potential candidates for normal tissue protection in the clinic. Of course additional work and a more complete survey of different nitroxides to identify the most effective agent will be required before these agents will be considered for the clinic. Studies have also been initiated to determine if the combination of **tempol** with the hematopoietic growth factor stem cell factor (SCF, c-kit ligand) would provide enhanced radiation protection in mice compared with the protection afforded by either agent alone. Treatment of mice pre- and post-radiation with SCF alone (100 ug/kg at -20, -4, and +4 hr) provided protection (76%) at 10 Gy and only 4% at 11 Gy. **Tempol** given 10 min prior to radiation protected (55%) mice from radiation doses up to 9 Gy. The combination of SCF and TP increased survival to 32% compared with only 2% survival with either agent alone (p less than 0.01) at 11 Gy. Thus, the combination of SCF and **tempol** may prove beneficial toward protecting normal tissues. Lastly, topical application of **tempol** has been shown to protect against radiation-induced alopecia (guinea pig model) both for single and multi-fractionated irradiation. The mechanism(s) of nitroxide-mediated radioprotection is at present unknown.

L4 ANSWER 67 OF 93 TOXLINE
ACCESSION NUMBER: 1994:55575 TOXLINE
DOCUMENT NUMBER: CRISP-94-CM06387-05
TITLE: DEVELOPMENT OF SUPEROXIDE DISMUTASE MIMICS.

AUTHOR: RUSSO A
CORPORATE SOURCE: NCI, NIH
U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, DIVISION OF CANCER TREATMENT.
CONTRACT NUMBER: 1Z01CM06387-05
SOURCE: (1992). Crisp Data Base National Institutes Of Health.
Award Type: A = Intramural Project
DOCUMENT TYPE: (RESEARCH)
FILE SEGMENT: CRISP
LANGUAGE: English
ENTRY MONTH: 199403

AB RPROJ/CRISP Our laboratory has shown that nitroxides, which have been used as EPR spin labels exhibit superoxide dismutase (SOD) activity and are quite effective agents in protecting cells against a wide variety of oxidative stresses. our lead compound, **Tempol**, a water soluble nitroxide has been shown to protect mammalian cells against superoxide generated from xanthine/xanthine oxidase, and direct hydrogen peroxide cytotoxicity. We have demonstrated that **Tempol** protects both cells in vitro and mice against ionizing radiation. Thus, the nitroxides represent a new class of radiation protectors that may have widespread use in protecting humans against radiation. Preliminary studies using a rodent **tumor** model have shown that **Tempol** does not protect **tumor** tissue. Further chemical characterization of the SOD mimic activity of nitroxides has revealed the presence of an oxoammonium cation intermediate. This information will be used to rationally screen a series of nitroxides for maximal protective capacity based on their oxidation potential and charge. **Tempol** has been shown to protect cells against mutation induction mediate /by superoxide, hydrogen peroxide, and radiation. **Tempol** has also been shown to protect cells exposed to various chemotherapy drugs including mitomycin C and SR- 4233. Not only might these agents be useful in protecting against certain chemotherapy agents but should be instructive in determining mechanisms of action. Topically applied, **Tempol** has been shown to protect against radiation-induced alopecia in guinea pigs. Since these agents readily penetrate cell membranes, they may be of use in other areas of medical research such as ischemia/reperfusion injury studies.

L4 ANSWER 68 OF 93 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 92156435 EMBASE
DOCUMENT NUMBER: 1992156435
TITLE: Hepatocyte toxicity of mechlorethamine and other alkylating anticancer drugs. Role of lipid peroxidation.
AUTHOR: Khan S.; Ramwani J.J.; O'Brien P.J.
CORPORATE SOURCE: Faculty of Pharmacy, University of Toronto, 19 Russell Street,Toronto, Ont. M5S 2S2, Canada
SOURCE: Biochemical Pharmacology, (1992) 43/9 (1963-1967).
ISSN: 0006-2952 CODEN: BCPCA6
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
048 Gastroenterology
052 Toxicology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The alkylating anticancer drugs, mechlorethamine (HN2), chlorambucil,

cyclophosphamide, carmustine and lomustine readily induced cytotoxicity in isolated rat hepatocytes. Hepatocyte glutathione (GSH) was depleted rapidly following addition of the drugs. Lipid peroxidation ensued following GSH depletion and before cytotoxicity occurred. Furthermore, cytotoxicity was delayed by the antioxidants butylated hydroxyanisole (BHA) and .alpha.-tocopherol, the ferric iron chelator desferoxamine or the radical trap 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPO) even when added 10 min later. HN2 was much less toxic to hepatocytes under nitrogen and caused much less lipid peroxidation than under aerobic conditions. Cytotoxicity induced by HN2 was also prevented by choline, suggesting that a choline carrier is responsible for HN2 uptake in the hepatocytes. Various sulfur compounds acted as antidotes for HN2 cytotoxicity. Thiosulfate was still effective when added 30 min after HN2. Depletion of GSH in the hepatocytes markedly increased their susceptibility to HN2. However, BHA, desferoxamine or TEMPO protected these hepatocytes from HN2. This suggests that antioxidants could prove useful in preventing the increased risk of hepatotoxicity if GSH-depleting agents are used to overcome **tumor** resistance to nitrogen mustards.

L4 ANSWER 69 OF 93 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 23
ACCESSION NUMBER: 1993:429 CAPLUS
DOCUMENT NUMBER: 118:429
TITLE: Effects of an inhibitor and a mimic of superoxide dismutase on bleomycin mutagenesis in Chinese hamster ovary cells
AUTHOR(S): An, Jie; Hsie, Abraham W.
CORPORATE SOURCE: Dep. Prev. Med. Community Health, Univ. Texas, Galveston, TX, 77550, USA
SOURCE: Mutat. Res. (1992), 270(2), 167-75
CODEN: MUREAV; ISSN: 0027-5107
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors have investigated the roles of reactive oxygen species (ROS) in bleomycin (BLM)-induced gene mutations in CHO cells using a superoxide dismutase (SOD) inhibitor, triethylenetetramine (TRIEN), and a SOD mimic, 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxy (**TEMPOL**), to lower and increase intracellular SOD activity, resp. Pretreatment of CHO cells with TRIEN (1 mM) for 1 h enhanced the mutagenic response of BLM (5-50 .mu.g/mL, 1 h treatment) in the hypoxanthine-guanine phosphoribosyltransferase (hprt) locus in CHO cell clone K1-BH4 (CHO/HPRT assay) and the xanthine-guanine phosphoribosyltransferase (gpt) gene in a CHO-K1 cell deriv. AS52 (AS52/GPT assay). Pretreatment with **TEMPOL** (1 mM) for 1 h decreased the BLM (20-100 .mu.g/mL, 1 h treatment) mutagenicity in the AS52/GPT assay. The mutagenic response of BLM appears to be modulated by the intracellular level of SOD activity and hence the intracellular level of ROS. These data provide further evidence for the involvement of ROS in bleomycin mutagenesis in mammalian cells.

L4 ANSWER 70 OF 93 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 91:672833 SCISEARCH
THE GENUINE ARTICLE: GU416
TITLE: MECHANISMS OF HYPOXIC AND AEROBIC CYTOTOXICITY OF MITOMYCIN-C IN CHINESE-HAMSTER V79 CELLS
AUTHOR: KRISHNA M C; DEGRAFF W; TAMURA S; GONZALEZ F J; SAMUNI A; RUSSO A; MITCHELL J B (Reprint)
CORPORATE SOURCE: NCI, RADIAT ONCOL BRANCH, CLIN ONCOL PROGRAM, BETHESDA, MD, 20892; NCI, MOLEC CARCINOGENESIS LAB, BETHESDA, MD, 20892; HEBREW UNIV JERUSALEM, SCH MED, JERUSALEM, ISRAEL

COUNTRY OF AUTHOR: USA; ISRAEL
SOURCE: CANCER RESEARCH, (1991) Vol. 51, No. 24, pp. 6622-6628.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 41

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Mitomycin C (MMC) induced aerobic and hypoxic cytotoxicity in Chinese hamster V79 cells was studied to evaluate the role of the 1-electron versus 2-electron reductive bioactivation. Superoxide dismutase, catalase, and desferal had no protective effects on the aerobic or hypoxic cytotoxicity of MMC, whereas **Tempol** and **Tempol**-H, which are known to interrupt and terminate radical reactions, provided partial protection under aerobic conditions. However, under hypoxic conditions, **Tempol** provided complete protection whereas **Tempol**-H was ineffective. Electron paramagnetic resonance and spin-trapping investigations, designed to study the mechanisms of such protective effects, confirmed that MMC is activated by the human NADPH:cytochrome P-450 oxidoreductase to its semiquinone radical and that, under aerobic conditions, the semiquinone radical reduces molecular oxygen. Under hypoxic conditions, the semiquinone of MMC reduces H2O2 to produce OH radicals as detected by electron paramagnetic resonance-spin trapping with 5,5-dimethyl-1-pyrroline N-oxide. The 1-electron reduced product of MMC was also found to reduce **Tempol** to the hydroxylamine, **Tempol**-H, whereas oxidation of **Tempol**-H by MMC approximately equal to was negligible.

Cell survival studies and electron paramagnetic resonance observations indicate that the hypoxic cytotoxicity of MMC is mediated by 1-electron activation to its semiquinone intermediate. Under aerobic conditions, the steady state concentration of this intermediate is low due to the facile autooxidation of the semiquinone producing O2 approximately equal to and H2O2 which are capable of causing oxidative cytotoxicity. **Tempol**, which can accept an electron from reducing radical species, completely inhibited the hypoxic cytotoxicity of MMC indicating MMC approximately equal to the semiquinone of MMC as the species responsible for DNA alkylation and selective hypoxic cytotoxicity of MMC. Our results also indicate that the aerobic cytotoxicity is mediated by other processes in addition to the 1-electron mediated activation.

L4 ANSWER 71 OF 93 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1992:120385 CAPLUS
DOCUMENT NUMBER: 116:120385
TITLE: DNA synthesis inhibition by nitroxide radicals in leukemia cells
AUTHOR(S): Liu, Lisheng; Zheng, Rongliang; Swartz, Harold M.; Zhang, Ziyi; Wei, Lulin
CORPORATE SOURCE: Dep. Biol., Lanzhou Univ., Lanzhou, 730000, Peop. Rep. China
SOURCE: Sci. China, Ser. B (1991), 34(9), 1063-9
CODEN: SCBSE5; ISSN: 1001-652X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Of 10 nitroxide-radical compds. tested, the most active in inhibiting DNA synthesis by and viability of isolated leukemia 7712 cells was 4-isothiocyanato-2,2,6,6-tetramethylpiperidine-1-oxyl. At 2.2 .mu.g/mL it inhibited cellular DNA formation by 50%. The inhibition by this compd., which contains both isothiocyanate and nitroxide groups, was greater than the sum of the inhibition by compds. contg. either of these groups alone. Redn. of the nitroxide moiety to hydroxylamine abolished the ability to inhibit DNA synthesis.

L4 ANSWER 72 OF 93 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1992:227771 CAPLUS
DOCUMENT NUMBER: 116:227771
TITLE: Nitroxyl radicals decrease toxicity of cytostatic agents
AUTHOR(S): Konovalova, N. P.; Dyachkovskaya, R. F.; Volkova, L. M.; Varfolomeev, V. N.
CORPORATE SOURCE: Inst. Chem. Phys., Chernogolovka, 142432, USSR
SOURCE: Anti-Cancer Drugs (1991), 2(6), 591-5
CODEN: ANTDEV; ISSN: 0959-4973
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Nitroxyl radicals of a series of piperidineoxyles and pyrrolinoxyles increase the tolerance of exptl. animals to the injection of otherwise LDs
of antitumor cytostatic agents. Simultaneous injection of nitroxyl radicals in different doses with 6-mercaptopurine, thiophosphamide, cyclophosphamide and the other cytostatic agents results in decreased toxicity and increased survival of animals. Nitroxyl radicals normalize the levels of the oxidized form of P 450 cytochrome that is decreased by the cytostatic agents.

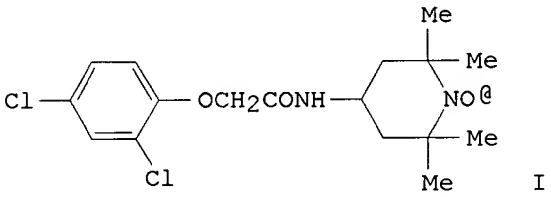
L4 ANSWER 73 OF 93 MEDLINE DUPLICATE 24
ACCESSION NUMBER: 91245792 MEDLINE
DOCUMENT NUMBER: 91245792
TITLE: Spin trap protection from **tumor** necrosis factor cytotoxicity.
AUTHOR: Pogrebniak H; Matthews W; Mitchell J; Russo A; Samuni A; Pass H
CORPORATE SOURCE: Thoracic Oncology Section, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892.
SOURCE: JOURNAL OF SURGICAL RESEARCH, (1991 May) 50 (5) 469-74.
Journal code: K7B. ISSN: 0022-4804.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199109
AB **Tumor** necrosis factor (TNF) facilitates superoxide production, and spin traps may detoxify superoxide by acting as superoxide dismutase mimics. We investigated the ability of a stable nitroxide spin trap, **TEMPOL**, to protect TNF-sensitive cells from exogenously added TNF. WEHI or L929 cells were incubated with TNF (500 units/ml) for 18 hr either
simultaneously with 0 to 8 mM **TEMPOL** or with the **TEMPOL** added at varying intervals after TNF exposure. A dose-dependent increase in survival was noted in the **TEMPOL**-treated cells, with 92 +/- 2% survival of WEHIs treated with 4 mM **TEMPOL** compared to 26 +/- 1% survival for non-**TEMPOL**-exposed cells (P2 less than 0.01). Significant increases in survival could be accomplished with as late as 15-hr delayed addition of the compound. The mechanism of protection does not seem to involve newly synthesized protein, and Northern blot analysis revealed that **TEMPOL** does not induce the genes for MnSOD or Cu-ZnSOD. The ability of **TEMPOL** to protect against TNF injury, even when exposure is delayed, may prove useful in conditions thought to be associated with free radical-lymphokine interactions such as ischemia-reperfusion, oxygen toxicity, or sepsis.

L4 ANSWER 74 OF 93 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:627496 CAPLUS
DOCUMENT NUMBER: 115:227496
TITLE: The mapping of three subfractions of endoplasmic reticulum membranes isolated from L-929 cells by the use of spin probes
AUTHOR(S): Mal'tseva, E. L.; Pal'mina, N. P.; Pryme, Ian F.

CORPORATE SOURCE: Inst. Chem. Phys., Moscow, USSR
SOURCE: Mol. Cell. Biochem. (1991), 106(1), 49-54
CODEN: MCBIB8; ISSN: 0300-8177
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The estn. of microviscosity parameters in smooth, light rough, and heavy rough endoplasmic reticulum subfractions isolated from L-929 cells is considered. ESR with 3 probes was used to make estns. of rotational correlation times. The highest microviscosity was found in the smooth fraction. The lipid bilayer is less viscous and the annular one more rigid in heavy rough compared to light rough membranes. The individual membrane subfractions differ with regard to their portrait of thermoinduced structural transitions. The highest no. of such transitions was detected in smooth membranes. There were no low temp. transitions (relative to physiol. temp.) or common thermoinduced structural rearrangements of the lipids in the heavy rough subfraction, a membrane fraction characteristic of transformed cells. Each membrane subfraction is characterized by an intrinsic series of thermoinduced structural transitions, which, in combinations with an estn. of microviscosity, yields a portrait of the structural state of the membrane lipids.

L4 ANSWER 75 OF 93 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:408525 CAPLUS
DOCUMENT NUMBER: 115:8525
TITLE: Synthesis of derivatives containing plant growth regulator moiety and nitroxyl radical moiety
AUTHOR(S): Zhu, Zhihong; Pan, Xinfu
CORPORATE SOURCE: Hunan Inst. Pharm. Ind., Changsha, 410014, Peop. Rep. China
SOURCE: Zhongguo Yiyao Gongye Zazhi (1990), 21(11), 491-3
CODEN: ZYGZEA; ISSN: 1001-8255
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
GI



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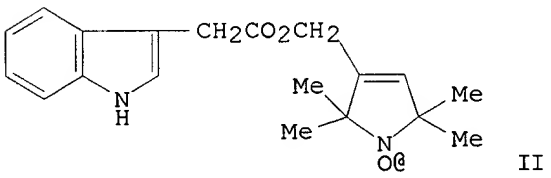


II

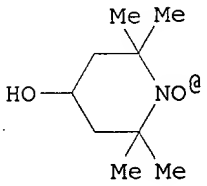
AB Nine new derivs. contg. plant growth regulator moiety and nitroxyl radical moiety were synthesized. Preliminary tests showed that the compds. I and II possessed in vitro inhibitory activity against P388 leukemia cell.

L4 ANSWER 76 OF 93 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1987:550397 CAPLUS
DOCUMENT NUMBER: 107:150397
TITLE: Radiosensitizers and thymine base damage
AUTHOR(S): Remsen, Joyce F.
CORPORATE SOURCE: Lab. Energy-Relat. Health Res., Univ. California,

David, CA, USA
SOURCE: NATO ASI Ser., Ser. A (1986), 124(Radiat. Carcinog. DNA Alterations), 467-9
CODEN: NALSDJ
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of 3 radiosensitizers, misonidazole, p-nitroacetophenone, and 4-hydroxy-2,2,6,6-tetramethylpiperidino-1-oxy (TMPN), on formation of thymine damage of the 5,6-dihydroxydihydrothymine type by irradn. with .gamma.-rays was characterized in HeLa cells. The 3 sensitizers have different electron affinities, or, in the case of TMPN, are a stable free radical. The formation of thymine base damage was measured in the presence of increasing concns. of each of the 3 sensitizers with and without 500 Gy of 60Co .gamma.-rays, at ice temp. Each sensitizer gave a different result. Increasing concns. of misonidazole suppressed the formation of base damage in air but had no apparent effect under hypoxia. In the presence of p-nitroacetophenone, similar amts. of base damage were formed under both aerobic and hypoxic conditions. TMPN, on the other hand, resulted in a complex pattern, with suppression at higher concns. (60 mM). The overall conclusion is that the sensitizers do not result in increased base damage but, if anything, suppress its formation. Therefore, the mechanism by which they sensitize under hypoxic conditions, such as found in solid **tumors**, is not by an increase in thymine base damage.

L4 ANSWER 77 OF 93 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 25
ACCESSION NUMBER: 1987:14473 CAPLUS
DOCUMENT NUMBER: 106:14473
TITLE: Mutagenicity of nitroxide free radicals
AUTHOR(S): Sies, Helmut; Mehlhorn, Rolf
CORPORATE SOURCE: Dep. Biochem., Univ. California, Berkeley, CA, USA
SOURCE: Arch. Biochem. Biophys. (1986), 251(1), 393-6
CODEN: ABBIA4; ISSN: 0003-9861
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



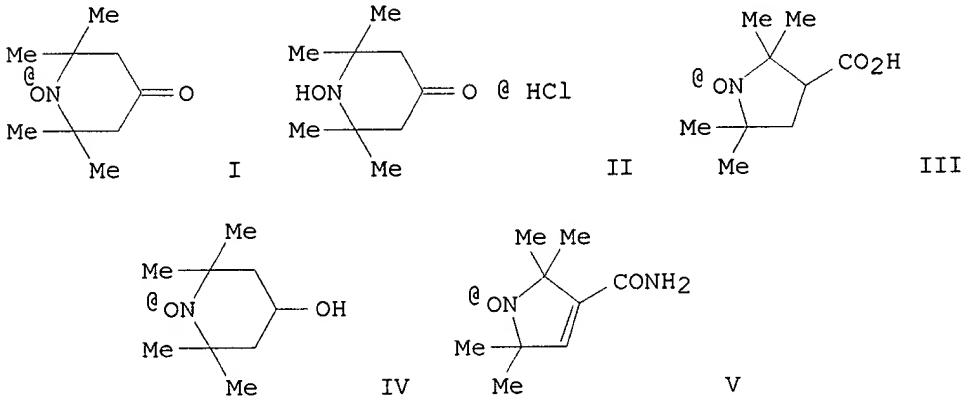
I

AB Stable nitroxides **tempol** (I) [**2226-96-2**] or PCAOL [2154-67-8] increased mutation rates in Salmonella typhimurium strain TA 104 (strain sensitive to oxidative damage) more than in strain TA 4124 (strain contg. the oxyR1 mutant allele for the defense against oxidative stress; it produces, e.g., high concns. of catalase and superoxide dismutase). The mutation rate in strain TA 104 increased by I plus superoxide (generated by xanthine oxidase and hypoxanthine) more than by I alone; strain TA 4124 mutation rate was not affected by the addn. of superoxide-generating systems. Mechanism of the nitroxides mutagenicity is suggested contg. sulfenyl hydroperoxides or subsequent oxidn. products as the active mutagenic species. This could be a model for the carcinogenicity of arom. amines.

L4 ANSWER 78 OF 93 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 86126317 EMBASE

DOCUMENT NUMBER: 1986126317
TITLE: Hypoxia-sensitive NMR contrast agents.
AUTHOR: Swartz H.M.; Chen K.; Pals M.; et al.
CORPORATE SOURCE: University of Illinois College of Medicine, Urbana, IL 61801, United States
SOURCE: Magnetic Resonance in Medicine, (1986) 3/1 (169-174). CODEN: MRMEEN
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
014 Radiology
027 Biophysics, Bioengineering and Medical Instrumentation
LANGUAGE: English

L4 ANSWER 79 OF 93 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1985:608776 CAPLUS
DOCUMENT NUMBER: 103:208776
TITLE: Suppression of plant **tumor** growth by inhibitors of free radical reactions
AUTHOR(S): Serebryanyi, A. M.; Morozova, I. S.; Krinitskaya, L. A.; Stom, D. I.; Zoz, N. N.
CORPORATE SOURCE: Inst. Chem. Phys., Moscow, USSR
SOURCE: Izv. Akad. Nauk SSSR, Ser. Biol. (1985), (5), 767-70 CODEN: IANBAM; ISSN: 0002-3329
DOCUMENT TYPE: Journal
LANGUAGE: Russian
GI



AB Topical application of 0.5% radical I [2896-70-0], or the product of its redn., the hydroxylamine II [22963-71-9], 1 wk after inoculation with Agrobacterium tumefaciens completely suppressed **tumor** growth in etiolated pea seedlings. Benzoquinone [106-51-4], quinhydrone [106-34-3], and esp. the radical III [2154-68-9] caused a complete and profound **tumor** regression without regrowth. Hydroquinone [123-31-9] and the radicals IV [**2226-96-2**] and V [3229-73-0] showed a moderate effectiveness. This is the 1st description of antitumor activity of stable nitroxyl radicals. The high effectiveness of the stable nitroxyl radicals and benzoquinone, which scavenge only alkyl radicals, indicate that these radicals, and not only the hydroperoxide radicals, are essential for the **tumor** growth. II acts probably as a prolonged-action form of I which is gradually oxidized to I by the atm. O.

L4 ANSWER 80 OF 93 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1986:440274 CAPLUS

DOCUMENT NUMBER: 105:40274
TITLE: In vitro reduction of spin labels by normal and neoplastic cells
AUTHOR(S): Sochanik, A. S.; Panz, T.; Lukiewicz, S. J.
CORPORATE SOURCE: Natl. Biomed. ESR Cent., Med. Coll. Wisconsin, Milwaukee, WI, 53226, USA
SOURCE: Ser. Fiz. (Uniw. im. Adama Mickiewicza Poznaniu) (1985), 54(Radio Microwave Spectrosc.), 475-8
CODEN: UPMFAS; ISSN: 0554-825X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The process of redn. of spin labels by various types of cells was studied under in vitro conditions using conventional ESR techniques. Three types of examd. cells were found to differ in their rate of reducing spin labels. Comparison of normal and neoplastic cells did not reveal any features specific for malignant transformation. The ability of cells to reduce spin labels depended on a no. of biol. properties (metab., phase of growth, permeability of membranes).

L4 ANSWER 81 OF 93 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1985:214639 CAPLUS
DOCUMENT NUMBER: 102:214639
TITLE: In the search for new anticancer drugs. XI. Anticancer activity of nitroxyl labeled phosphoric N,N;N',N';N",N"-tris[1,2-ethanediyl]triamide(TEPA) and phosphorothioic N,N;N',N';N",N"-tris[1,2-ethanediyl]triamide(thio-TEPA) derivatives
AUTHOR(S): Sosnovsky, George; Li, Shu Wen
CORPORATE SOURCE: Dep. Chem., Univ. Wisconsin, Milwaukee, WI, 53201, USA
SOURCE: Cancer Lett. (Shannon, Irel.) (1985), 25(3), 255-60
CODEN: CALEDQ; ISSN: 0304-3835
DOCUMENT TYPE: Journal
LANGUAGE: English
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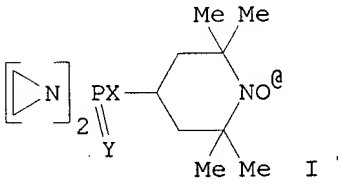

I

AB In order to further evaluate the effect of the nitroxyl moiety on the anticancer activity of nitroxyl-labeled analogs of phosphoric N,N,N',N',N'',N''-tris[1,2-ethanediyl]triamide (TEPA) and phosphorothioic N,N,N',N',N'',N''-tris[1,2-ethanediyl]triamide] (thio-TEPA) [52-24-4]I (X = O, NH, or NHCO2; Y = O or S), the activity of these compds. was compared in vivo, using murine lymphoid leukemia L1210, with the reduced forms of the drugs, i.e. the hydroxylamines and amine congeners. At optimum dose, all compds. were active. However, the nitrosyl contg. compds. were more active than the corresponding reduced forms. An admixt. of 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl [**2226-96-2**] had no effect on the activity of thio-TEPA. Consequently, the nitroxyl moiety must be an integral part of the anticancer drug's structure in order to influence that drug's performance.

L4 ANSWER 82 OF 93 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1985:469158 CAPLUS
DOCUMENT NUMBER: 103:69158
TITLE: Differences in the reduction kinetics of incorporated spin labels in undifferentiated and differentiated mouse neuroblastoma cells
AUTHOR(S): Chen, Kuang Yu; McLaughlin, Michael G.
CORPORATE SOURCE: Dep. Chem., Rutgers, State Univ. New Jersey, New Brunswick, NJ, 08903, USA
SOURCE: Biochim. Biophys. Acta (1985), 845(2), 189-95
CODEN: BBACAQ; ISSN: 0006-3002
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Significant differences in the rate of redn. of 2 spin labels, 5-doxylstearic acid and **TEMPOL**, in the undifferentiated and differentiated NB-15 mouse neuroblastoma cells were demonstrated by using ESR (EPR) spectroscopy. The half-time (T1/2) values for decay of the EPR signal of 5-doxylstearic acid in the undifferentiated and differentiated neuroblastoma cells were 70 min and 290 min, resp. The T1/2 values of **TEMPOL** in the undifferentiated and differentiated cells were 18 min and 34 min, resp. The cellular reductant was characterized as non-protein-bound sulfhydryl groups. A corresponding difference in the cellular non-protein-bound sulfhydryl content, 19.30 nmol/mg protein for the undifferentiated cells and 6.78 nmol/mg protein for the differentiated cells, was obsd. In the undifferentiated cells, the permeation of non-protein-bound sulfhydryl compds. from the cytosol to membrane may be responsible for the redn. of the lipid-sol. stearic acid spin labels.

L4 ANSWER 83 OF 93 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1985:400198 CAPLUS
DOCUMENT NUMBER: 103:198
TITLE: Electronic parameters and molecular mechanisms of biological action of nitroxyl radicals
AUTHOR(S): Luzhkov, V. B.
CORPORATE SOURCE: Inst. Chem. Phys., Chernogolovka, 142432, USSR
SOURCE: THEOCHEM (1985), 22, 165-72
CODEN: THEODJ; ISSN: 0166-1280
DOCUMENT TYPE: Journal
LANGUAGE: English
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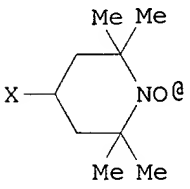

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AB The electronic parameters of radical, anion and hydroxylamino forms of a series of substituted 2,2',6,6'-tetramethyl-4-X-piperidine-1-oxyls (I; X = OH, H, O, CH2NH2, PhNHCO2, etc.) are calcd. at the INDO level. The energetics of the interaction with the water mol. were evaluated by averaging the electrostatic energy of interaction (calcd. in dipole approxn.) over the Van-der-Waals surface envelope of the nitroxyl radicals. The study of structure-activity relations shows that the toxicity of these compds. depends on their transport and redox properties.

It is concluded that the toxicity of these nitroxyl radicals is probably